Double-Blind Placebo-Controlled Administration of Fluoxetine in Restricting- and Restricting-Purging-Type Anorexia Nervosa

Walter H. Kaye, Toshihiko Nagata, Theodore E. Weltzin, L.K. George Hsu, Mae S. Sokol, Claire McConaha, Katherine H. Plotnicov, Jeff Weise, and Dianne Deep

Background: *Anorexia nervosa is an often chronic disorder with high morbidity and mortality. Many people relapse after weight restoration. This study was designed to determine whether a selective serotonin reuptake inhibitor would improve outcome and reduce relapse after weight restoration by contributing to maintenance of a healthy normal weight and a reduction of symptoms.*

Methods: *We administered a double-blind placebo-controlled trial of fluoxetine to 35 patients with restricting-type anorexia nervosa. Anorexics were randomly assigned to fluoxetine (*n = *16) or a placebo (*n = *19) after inpatient weight gain and then were observed as outpatients for 1 year.*

Results: *Ten of 16 (63%) subjects remained on fluoxetine for a year, whereas only three of 19 (16%) remained on the placebo for a year (*p = *.006). Those subjects remaining on fluoxetine for a year had reduced relapse as determined by a significant increase in weight and reduction in symptoms.*

Conclusions: *This study offers preliminary evidence that fluoxetine may be useful in improving outcome and preventing relapse of patients with anorexia nervosa after weight restoration.* Biol Psychiatry 2001;49:644–652

Key Words: Anorexia nervosa, fluoxetine, SSRI, relapse prevention

Introduction

Anorexia nervosa (AN) (American Psychiatric Association 1994) is a disorder of unknown etiology that predominantly occurs in women. This illness is characterized by restricted eating, the relentless pursuit of thinness, and obsessive fears of being fat. These symptoms result in profound weight loss and considerable psychologic morbidity.

Because of limited efficacy of existing treatments (Herzog et al 1992), many people with AN have a chronic, relapsing illness (Hall and Crisp 1987; Hsu 1980; Theander 1983). Moreover, AN has the highest death rate of any psychiatric disorder (Sullivan 1995). Still, extended hospitalizations can be lifesaving because such treatment can restore weight to emaciated individuals, which, in turn, reverses medical complications (Hsu 1988; Patton 1988). However, such hospitalizations can be lengthy and expensive. In fact, the hospital utilization rate for people with AN is higher than for any other psychiatric disorder, aside from schizophrenia and organic mental disorders (McKenzie and Joyce 1992). However, short-term weight restoration has had limited effect on future outcome (Hall and Crisp 1987; Hsu 1980; Theander 1983). For example, the Maudsley study (Russell et al 1987) reported that only 23% of the patients had a good outcome at 1 year after hospitalization for weight restoration.

The first generation of treatment studies focused mainly on attempts to increase the rate of weight gain of emaciated patients in a hospital setting. Controlled trials of neuroleptics (Vandereycken 1984; Vandereycken and Pierloot 1982) and earlier generations of antidepressants (Biederman et al 1985; Halmi et al 1986; Lacey and Crisp 1980) had little effect on the rate of weight gain. Inpatient treatment, consisting of nursing care, behavior modification, and supportive psychotherapy, succeeds in restoring the weight of most emaciated anorexics. Thus, it is difficult to prove that an active medication is effective in such a setting. A second generation of studies has inves-

From the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (WHK, TN, TEW, LKGH, MSS, CM, KHP, JW, DD), the Department of Neuropsychiatry, Osaka City University Medical School, Osaka, Japan (TN), the Department of Psychiatry, University of Wisconsin, Madison (TEW), the Department of Psychiatry, Tufts University School of Medicine, Boston, Massachusetts (LKGH), and Eating Disorders Program, Menninger Clinic, Topeka, Kansas (MSS).

Address reprint requests to Walter H. Kaye, M.D., University of Pittsburgh, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, E-724, Pittsburgh PA 15213.

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tigated psychotherapies specifically developed to treat AN. Several of these studies have suggested that specialized treatment reduced relapse at 1- to 2-year follow-ups after initial treatment (Gowers et al 1994; Treasure et al 1995) or improved outcome in subgroups of patients (Russell et al 1987).

To our knowledge, there have been no controlled pharmacotherapy studies that have focused on relapse prevention. Our group (Kaye et al 1991) administered an open trial of fluoxetine to 31 women with AN in an outpatient setting after weight restoration. At the time of follow-up (11 [SD 6] months on fluoxetine), 29 of the 31 patients had maintained their weight at or above 85% average body weight (ABW) (Metropolitan Life Insurance Company 1959) (97% [SD 13%] ABW for the group). In this study, response was good in 10, partial in 17, and poor in four patients with AN as measured by improvements in eating behavior, mood, and obsessional symptoms. Restricting-type AN patients responded significantly better than bulimic and/or purging-type patients with AN. This open trial suggested that fluoxetine may help prevent relapse after weight restoration in individuals with AN.

To test this finding, we designed a double-blind, placebo-controlled trial of fluoxetine in AN. The primary aim of this study was to investigate whether fluoxetine would improve outcome over a 52-week period in a group of outpatients with restricting-type AN. Subjects were started on fluoxetine after they achieved weight restoration during a hospitalization. Our other aim was to determine whether fluoxetine was useful because of its effects on core eating disorder symptoms, obsessionality, or depression. It is well recognized that many patients with AN have comorbid depression (Strober and Katz 1988) and obsessive-compulsive disorder (Thiel et al 1995). These symptoms, which are exaggerated by weight loss, are modestly improved after weight restoration (Channon and DeSilva 1985; Eckert et al 1982; Laessle et al 1988; Pollice et al 1997; Stonehill and Crisp 1977). Fluoxetine has been shown to be an effective drug for reducing depression (Benfield et al 1986) and compulsive behaviors (Piccinelli et al 1995).

Methods and Materials

Subjects

After receiving a complete description of the study, all subjects gave informed consent. All subjects who entered this study, except one, were admissions to the inpatient eating disorders treatment program at the Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center. All subjects were female and met DSM-IV criteria for AN when they were underweight. To obtain a sufficient sample size, this study included patients with AN with a history of weight loss due to restrictive eating behavior as well as patients with AN who restricted and purged. However, no subjects had binged during their lifetime. Patients were excluded if they had concurrent severe medical or neurologic illness, concurrent or previous schizophrenic illness, or concurrent or recent (within the last 12 months) alcohol or substance dependence disorder. In the month before entry into this study, subjects did not use psychotropic medication, except for a small amount of alprazolam (up to 1.0 mg/day). Although several subjects remained on alprazolam during the initial few weeks of treatment in the hospital, no subject was given alprazolam after discharge from the hospital.

Treatment Trial

We asked 95 subjects, who were admitted to the eating disorder inpatient unit and who met the inclusion criteria and none of the exclusion criteria, to be in this study. All but one subject began this study while hospitalized on the inpatient eating disorder treatment unit. During this course of inpatient treatment, all subjects received the same program of intensive cognitive behavioral, individual, and dietary therapy. Our intent was to start subjects on fluoxetine or a placebo 2 to 4 weeks before discharge. However, due to insurance limitations that shortened length of stay, some subjects were started on the medication trial during refeeding and before complete weight restoration (90% ABW). Subjects were randomized to fluoxetine or placebo conditions after being separated into two groups by weight (either $>$90% ABW or $<$89% ABW). Of the subjects included in this analysis, 34 were inpatients; of these, 19 (56%) subjects were started on medication (nine fluoxetine, 10 placebo) after reaching 90% ABW, seven (21%) were in the range of 85 to 89% ABW (three fluoxetine, four placebo), and six (18%) anorexics were in the range of 80% to 84% ABW (three fluoxetine, three placebo). One subject was started on fluoxetine at 78% ABW and one subject was started on placebo at 76% ABW. Only one AN subject began treatment while an outpatient (82% ABW). The range of weight for all subjects at the start of the study was 76% to 100% ABW.

Subjects were begun on one capsule (20 mg fluoxetine or a placebo) per day. Dosage over the next 52 weeks was adjusted by a physician who was blind to the patient's assignment in accordance with written structured assessment and treatment guidelines designed before the start of the study. An increase in medication dose (one capsule, 20 mg) was made only at monthly intervals because of the long half-life of fluoxetine and its metabolite (Benfield et al 1986; Gram 1994). The dose could be decreased at any visit. The dose range was one capsule every other day (minimum) to three capsules a day (maximum).

After discharge from the hospital, subjects were evaluated in person at 4-week intervals for as long as they remained in the study (up to 52 weeks). If the subject's condition deteriorated, she was evaluated on a weekly basis. These evaluations were conducted in person by physicians (LKGH, TEW, MSS), a research nurse (CM), and several trained clinicians (KHP, JW, DD) experienced in the treatment of AN who were blind to the patient's medication status and who followed the structured assessment and treatment guidelines. Subjects were weighed on a calibrated balance-beam scale in the WPIC outpatient clinic by

staff. If subjects missed outpatient sessions, they were contacted by phone by staff for evaluation and assessment.

In designing this study, it was thought that most subjects lived too far from our center (approximately 60% of inpatients lived more than 100 miles from Pittsburgh) to travel to Pittsburgh regularly to take part in a frequent, intensive, and standardized course of outpatient psychotherapy after discharge from the hospital. However, subjects could engage in outpatient psychotherapy if they so desired. Three subjects had regular outpatient therapy by outside therapists in addition to outpatient clinic visits at WPIC. Two were on fluoxetine (they both dropped out) and one was on a placebo (she dropped out). Nine of the subjects attending the WPIC outpatient clinic received more regular and intensive psychotherapy from staff. Three were on fluoxetine and all completed a year in the study. Six were on a placebo and all dropped out. One subject who lived at some distance was unable to come to Pittsburgh for sessions. She was observed by her family doctor, who saw her weekly in his office, where he weighed her and provided support but no psychotherapy. She was assessed on the telephone. This subject was on fluoxetine and dropped out of the study. The other 23 subjects did not receive any regular psychotherapy.

All subjects were instructed to consume a healthy diet and maintain a normal body weight. They were given guidelines for continued study participation including maintenance of a normal body weight, adequate functioning at home and in school or work, and the absence of substantial core eating disorder symptoms, obsessions, or mood disturbances that interfered with their school, work, and social functioning. Patients were instructed to call the clinic if side effects developed between sessions or if they became more depressed, hopeless, or suicidal.

Primary Aim and Outcome Measure

The primary aim was to determine whether fluoxetine improved outcome and prevented relapse in comparison to a placebo for 1 year after discharge from hospital treatment. Because of the difficulty of getting AN subjects to agree to participate in a year-long drug trial of relapse prevention, subjects and their relatives were informed that it was possible that fluoxetine would improve eating or reduce drive for thinness, dysphoric mood, and/or obsessions, and thus improve the ability to function and reduce the possibility of relapse. We asked them to take fluoxetine or the placebo for at least 4 weeks. Subjects were informed that they could drop out of the study if they were no better or getting worse over the course of outpatient follow-up. We were concerned that substantial and perhaps life threatening weight loss might occur if subjects were asked to complete a year-long study using a noneffective treatment. Thus, a subject's participation in the study was terminated if she had substantial and incapacitating symptoms, since we did not want to risk subjects' lives by substantial weight loss. Consequently, dropout from the study was most often decided by the subject and/or her relatives, as well as by the blind treating physician who terminated the study if there was a deteriorating clinical course (i.e., incapacitating preoccupations with thinness or pathologic eating behavior, substantial weight loss, incapacitating obsessionality, depression, or anxiety). Thus, we assessed whether patients were "treatment completers" or "treatment dropouts." Patients were considered to be treatment completers if they remained on fluoxetine during the duration of the 1-year follow-up. To calculate the time of substantial symptoms, we used the date of the follow-up visit during which the end point was documented.

Secondary Aim and Outcome Measures

The secondary aim of the study was to determine whether fluoxetine produced a significant reduction in depression, anxiety, obsessions, or core eating disorder behavior or increase in weight, as compared with a placebo. The outcomes measures for this aim were change scores from baseline to termination on standardized assessments of these symptoms or weight during clinic visits. These assessments were conducted at baseline before beginning medication and at monthly intervals by doctoral- or masters-level psychologists who were blind to the patient's medication status. The instruments included the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), the Hamilton Anxiety Rating Scale (Hamilton 1959), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al 1989a, 1989b), and the Y-BOCS-ED. The Y-BOCS was used to assess only classic obsessive–compulsive symptoms typical of patients with OCD. Obsessions and compulsions specific to core eating disorder symptoms (body image distortions, pathologic eating, exercise, etc.) were assessed by the Y-BOCS-ED, a version of the Y-BOCS similar to an assessment standardized by others (Sunday et al 1995). Exit interviews were completed within 4 weeks of the time that subjects ended the study.

Data Analysis

A total of 39 women with restricting-type AN, with or without purging behavior, entered this study. They were randomly assigned to fluoxetine (19 subjects) or a placebo (20 subjects). Data on four subjects were excluded from this analysis. Three subjects were excluded because the blind was broken and the data were analyzed before the subjects, each of whom was taking fluoxetine, had completed the year of outpatient follow-up. Although they were doing well, their data were excluded from this analysis because the study was terminated before a year of follow-up. A fourth subject, who was on the placebo, dropped out of the trial after only 15 days of treatment, and thus her data were not included in this analysis because we included only subjects who took fluoxetine or a placebo for at least 30 days. Thus, findings for a total of 35 subjects are discussed in this study. The principal analysis for the primary outcome measure was a survival analysis (Cox and Oakes 1984; Kalbfleisch and Prentice 1980). The principal analyses for the secondary outcome measures were based on a three-factor design (treatment, success/failure, time) with repeated measures on one of the three factors (two time periods). The analyses follow the design in Winer (1971) section 7.4, and were done using BMDP procedure 4V (Winer 1971). Paired *t* tests were also used to compare baseline and end point values. Values are expressed as mean (SD).

Table 1. Clinical Information at Baseline for Groups Assigned to Fluoxetine and a Placebo

	Fluoxetine	Placebo	*t* value	*p*
N	16	19		
Age	23 (SD 9)	22 (SD 6)	0.42	ns
Age of onset	16 (SD 5)	18 (SD 5)	0.64	ns
% ABW at entry	89 (SD 6)	89 (SD 7)	0.07	ns
Low lifetime % of ABW	70 (SD 8)	73 (SD 7)	0.94	ns
High lifetime % ABW	110 (SD 24)	112 (SD 16)	0.26	ns
HDRS at entry	13.7 (SD 10.7)	13.9 (SD 10.4)	0.05	ns
HARS at entry	11.3 (SD 7.5)	11.2 (SD 6.4)	0.04	ns
Y-BOCS at entry	15.0 (SD 10.1)	14.3 (SD 7.7)	0.23	ns
Y-BOCS-ED at entry	20.9 (SD 11.2)	20.5 (SD 9.5)	0.48	ns

Comparison by group *t* test. df = 33 for all comparisons. ABW, average body weight; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; Y-BOCS-ED, Y-BOCS–derived Eating Disorder Scale.

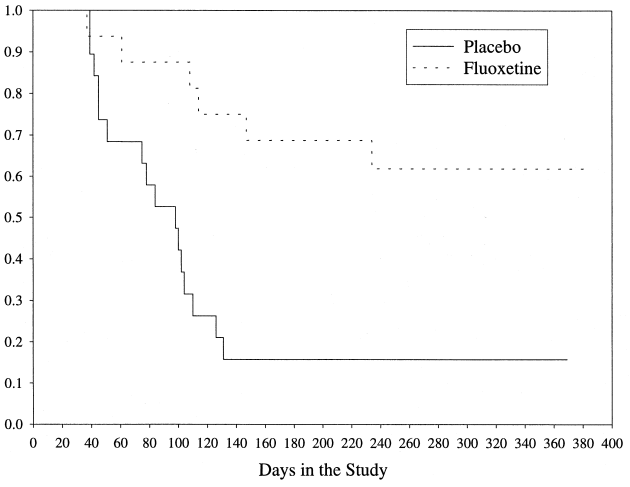

Figure 1. Survival curve for subjects with anorexia nervosa treated with fluoxetine or a placebo. The y axis is proportionate to the number of subjects remaining in the study.

Results

Before the study, the 16 subjects on fluoxetine and 19 subjects on a placebo (Table 1) had similar current percent ABWs, past low and high percent ABWs, ages, ages of onset, and levels of depression, anxiety, obsessions and compulsions, and core eating disorder symptoms.

Ten (63%) of the 16 subjects given fluoxetine but only three (16%) of the 19 subjects given a placebo remained in the study for 1 year (Table 2). There was a significant difference between these groups ($p = .006$) by Fisher exact test. One patient in the fluoxetine group terminated the study on day 213 because she was in an automobile accident that caused a prolonged coma. She had responded well until that accident, so she was considered as part of the treatment completer group. A survival analysis (Figure 1) showed a significant difference [log-rank (1) = 10.0, $p = .002$] in subjects who completed the study on fluoxetine relative to those subjects on a placebo.

Of the 35 subjects who completed the study, 20 had pure restricting-type AN. There was a trend for more fluoxetine subjects completing the study (78%, 7/9) than placebo subjects (27%, 3/11) ($p = .07$, Fisher exact test) for this subgroup. Similarly, 15 subjects with restricting-type AN who purged (by laxatives and/or vomiting) but did not binge showed a trend ($p = .08$, Fisher exact test) for completing the study on fluoxetine (42%, 3/7), as compared with the placebo (0/8).

Table 2. Comparison of Completion of Subject Groups

	Fluoxetine	Placebo
Completers	10	3
Dropouts	6	16

There was a significant difference between these groups ($n = .006$) by Fisher exact test.

For the most part, subjects themselves, or their significant others, made the decision as to when to drop out of the study. This decision tended to be made because they had symptoms indicating that they were relapsing and thus they requested termination from the study. For the 16 subjects on the placebo who dropped out of the study, the decision was made for five by the blind physician and for 11 by the subject herself or her relatives. For the six subjects on fluoxetine who dropped out of the study, the blind physician decided for two, and for four, the decision was made by the subject or her relatives. For those on the placebo, four terminated because of substantial weight loss, two because of persistent depressive symptoms, and 10 because of persistent eating disorder symptoms such as restricted eating, eating rituals, etc. For those on fluoxetine, three terminated because of substantial weight loss, one because of persistent depressive symptoms, and two because of persistent eating disorder symptoms. Assessments were obtained within 4 weeks of termination of the trial for all completers and for all but three of the dropout subjects. Some subjects who dropped out did not have all assessments completed because all assessments were not done at each assessment interval and they did not return for further assessment. The total number of subjects for the various analyses is reflected in the degrees of freedom in Tables 3 and 4.

Response to Treatment

We compared four groups of subjects after they were segregated by drug status (fluoxetine vs. placebo) and completer versus dropout status (Tables 3 and 4). At baseline, these four groups had similar ages and body weights as well as ages of onset and highest and lowest

Table 3. Comparison of Days in the Study and Dose of Fluoxetine at the End of the Study

	Fluoxetine treatment completers	Fluoxetine treatment dropouts	Placebo treatment completers	Placebo treatment dropouts	df	*F* value	*p*
N	10	6	3	16			
Days in study	352 (SD 5)	116 (SD 69)	368 (SD 2)	79 (SD 32)	3,31	97.45	.0001
Dose at end of study (mg)	38 (SD 21)	43 (SD 15)	36 (SD 21)	36 (SD 13)	3,31	0.34	.80

Days in study and dose compared by one-way analysis of variance.

percent ABWs in their lifetime (data not shown). The four groups of subjects were prescribed similar doses of fluoxetine or a placebo (Table 3). At the time of their exit from the trial, those who completed the study and those who dropped out of the trial on fluoxetine had similar blood levels for fluoxetine (274 [SD 242] vs. 400 [SD 360] ng/mL; $t = 0.75$, ns) and norfluoxetine (254 [SD 144] vs. 462 [SD 410] ng/mL; $t = 0.39$, ns). Outcome for those subjects engaging in psychotherapy was similar to outcome for those subjects not engaging in psychotherapy.

The four groups showed a significant time × drug × status interaction for the Y-BOCS score and a trend for the HDRS (Table 4). This analysis did not show differences in weight, HARS score, or Y-BOCS-ED-derived score for eating disorder-related obsessions and compulsions. However, by paired *t* test, only the group that remained on fluoxetine for a year showed a significant difference, or trend, between baseline and the end of the study, in terms of increase in weight and reductions in depression, anxiety, obsessions and compulsions, and core eating disorder symptoms.

The subjects on the placebo who dropped out of the study did so by 130 days into the trial. As a group, this cohort showed no change in weight or symptoms at the time they dropped out relative to baseline. Not all subjects agreed to reassessment at the end of their trial. Three subjects on fluoxetine who dropped out and four people on the placebo who dropped out refused to provide an exit weight, so we used the weight obtained 4 weeks previously. Thus, these data may not accurately reflect measures such as weight in this cohort of subjects.

Discussion

This is the first controlled study that supports the possibility that a pharmaceutical therapy is effective in improving outcome in AN. Sixty-three percent of subjects completed a 1-year trial of fluoxetine, whereas 16% of subjects

Table 4. Weight and Assessment Scores for Each Cell

	Fluoxetine treatment completers	Fluoxetine treatment dropouts	Placebo treatment completers	Placebo treatment dropouts	df	Drug	Status	Drug × status	Time	Time × drug	Time × status	Time × drug × status
% ABW at start	88 (SD 7)	92 (SD 5)	89 (SD 12)	90 (SD 6)								
Change in % ABW at end of study relative to baseline	5.3 (SD 5.3)[a]	−1.2 (SD 3.3)	11.2 (SD 11.9)	−0.2 (SD 6.7)	1,31	.6117	.3409	.2559	.0065	.1907	.0017	.3571
HDRS at start	13.4 (SD 9.7)	14.3 (SD 13.1)	4.0 (SD 5.3)	15.8 (SD 10.0)								
Change of HDRS	−8.2 (SD 7.9)[a]	0.3 (SD 8.1)	1.7 (SD 2.1)	−3.5 (SD 10.5)	1,25	.3423	.0389	.7456	.2092	.4254	.6586	.0816
HARS at start	10.6 (SD 1.7)	12.5 (SD 4.4)	5.3 (SD 3.9)	12.3 (SD 1.5)								
Change of HARS	−5.1 (SD 1.6)[a]	−0.8 (SD 5.6)	−2.0 (SD 1.7)	−2.4 (SD 1.9)	1,28	.2608	.0385	.8091	.0499	.7725	.4488	.2561
Y-BOCS total at start	16.8 (SD 9.6)	12.0 (SD 11.2)	8.0 (SD 8.5)	15.5 (SD 7.2)								
Change of Y-BOCS	−8.6 (SD 12.7)[b]	8.6 (SD 7.2)[b]	−1.0 (SD 5.6)	−1.6 (SD 6.9)	1,26	.6871	.2629	.2629	.7460	.7460	.0450	.0329
Y-BOCS ED total at start	21.2 (SD 11.2)	20.3 (SD 13.3)	25.7 (SD 2.9)	19.5 (SD 10.1)								
Change of Y-BOCS ED	−8.4 (SD 11.1)[c]	4.2 (SD 7.4)	−14.3 (SD 13.7)	0.8 (SD 10.8)	1,26	.7908	.5522	.8822	.0605	.3101	.0052	.7863

Percent average body weight (% ABW), HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; Y-BOCS-ED, and Y-BOCS-Derived Eating Disorder Scale compared by a three-factor design (treatment, response/nonresponse, time) with repeated measures on one of the three factors (two time periods). The *p* value is shown for factors and factor interactions.

[a] $p < .01$, baseline vs. change at end of study by paired *t* test.

[b] $p < .1$, baseline vs. change at end of study by paired *t* test.

[c] $p < .05$, baseline vs. change at end of study by paired *t* test.

completed a 1-year trial on a placebo. Only the subjects who remained on fluoxetine for a year had a significant increase in weight and reduction in core eating disorder symptoms, obsessive thoughts, and depressed and anxious mood. Our findings are supported by several open trials (Gwirtsman et al 1990; Kaye et al 1991), which have shown that fluoxetine improves outcome in people with AN, although a recent retrospective study failed to show a significant fluoxetine effect (Strober et al 1997). Limited evidence also suggests that other serotonin-specific medications are useful in this disorder (Crisp et al 1987; Halmi et al 1986).

Clinically, most subjects did poorly on the placebo and dropped out of treatment. Our rate of treatment failures on the placebo was comparable to the Maudsley study (Russell et al 1987), in which only 23% of the patients had a good outcome at 1 year after discharge, despite intensive outpatient, individual, or family therapy. We designed our study so that subjects, or their family members, could terminate the treatment trial if they had a deteriorating clinical course. Subjects terminated the trial for a variety of reasons, including weight loss and persistence of depression or core eating disorder symptoms. The major reason given for dropping out of the placebo cell was restricted eating and incapacitating core eating disorder symptoms. Many of these subjects dropped out before experiencing substantial weight loss. For ethical and pragmatic reasons, we did not want subjects to lose substantial body weight by asking them to continue with an ineffective treatment.

Only three placebo subjects successfully completed treatment. Although this group was too small for us to draw firm conclusions, these data may offer some clues as to why a small number of patients with AN do not relapse after weight restoration. These groups were well matched before the start of the study (Table 1). Subjects that did well on a placebo had lower baseline scores for depression and anxiety. Perhaps good outcome in AN is associated with reduced burden of comorbid psychiatric symptoms.

About one third of patients dropped out of the trial while on fluoxetine. Clinically, these people appeared to have a poor response. Although this was not assessed, given the typical symptom patterns of AN it is possible that subjects who did poorly on fluoxetine continued to have poor dietary intake after discharge from the hospital. Several lines of evidence raise the possibility that malnutrition may neutralize the therapeutic actions of selective serotonin reuptake inhibitors (SSRIs). Tryptophan, an essential amino acid that can only be obtained from food, is the precursor of serotonin. In healthy women, dieting significantly lowers plasma tryptophan, the precursor of serotonin (Anderson et al 1990), resulting in a decreased plasma ratio of tryptophan to neutral amino acids and, in turn, a reduction in the availability of tryptophan to the brain, and decreased brain serotonin synthesis (Gibbons et al 1979; Messing et al 1976). Depletion of tryptophan, the precursor of serotonin, reverses the effects of antidepressants in depressed patients (Delgado et al 1990). In support of the possibility that malnutrition may prevent patients emaciated with AN from responding to SSRIs, recent studies show that SSRIs have little effect on reducing symptoms and preventing hospitalization in underweight AN subjects (Attia et al 1998; Ferguson et al 1999). Women with AN, when malnourished and underweight, have reduced plasma tryptophan availability (Schweiger et al 1986) and reduced cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) (Kaye et al 1988), the major metabolite of serotonin in the brain. In addition, low estrogen values during the malnourished state may reduce serotonin activity by effects on gene expression for serotonin receptors (Fink and Summner 1996) or the serotonin transporter (McQueen et al 1996). Selective serotonin reuptake inhibitors are dependent on neuronal release of serotonin for their action. If malnourished anorexics have compromised release of serotonin from presynaptic neuronal storage sites and reduced synaptic serotonin concentrations, then a clinically meaningful response to an SSRI might not occur (Tollefson 1995). The possibility that fluoxetine is only effective for anorexics after weight restoration is supported by the fact that a change of serotonin activity is associated with weight gain. For example, CSF 5-HIAA levels are low in underweight AN subjects, normal in short-term weight-restored AN subjects, and elevated in long-term weight-restored AN subjects (Kaye et al 1984). If CSF 5-HIAA levels accurately reflect central nervous system serotonin activity, then these data imply that a substantial increase in serotonin activity occurs after weight gain. In addition, four of six cohorts studied have found an association of a polymorphism (−1438G/A) in the promoter region of the gene for the serotonin 2A (5-HT_{2A}) receptor with AN (Campbell et al 1998; Collier et al 1997; Enoch et al 1998; Hinney et al 1997; Sorbi et al 1998). Efficacy of antidepressant medication is temporally correlated with changes in 5-HT_{2A} activity (Yates et al 1990). Whether this receptor influences fluoxetine response in some AN remains to be determined.

Fluoxetine and other medications that act on serotonin have been shown to be effective in bulimia nervosa (BN) (Mitchell et al 1993; Walsh 1995). No subject in this study had a lifetime history of BN. Still, studies of familial aggregation (Lilenfeld et al 1998) and twin studies (Kendler et al 1991) suggest that AN and BN share some etiologic vulnerability. Moreover, AN and BN share a disturbance of serotonin activity that may create a vulnerability for the expression for symptoms that are common

to these illnesses (Kaye et al 1984; Srinivasagam et al 1995).

This study has a number of limitations. First, the sample size was small. In addition, to enroll sufficient numbers of subjects in a relatively timely manner, we had to make several compromises. For example, pure restricting-type AN patients and restricting/purging-type AN patients were considered together. Additionally, subjects were enrolled from a large geographic region so that it was not possible for subjects to have standardized outpatient psychologic treatment along with the medication trial. We encouraged subjects to drop out of the trial if they were doing poorly, since we were concerned that a worsening clinical state might result in extreme malnutrition and weight loss, and even death. Encouraging people to leave the study before substantial weight loss had occurred on fluoxetine or a placebo might raise questions as to whether these subjects actually experienced a full-blown relapse. Subjects were assessed by blind structured interview to determine when subjects were deteriorating to minimize any drug versus placebo bias. Importantly, for most subjects who dropped out of the study, they or their parents made the decision to terminate the study. This study supports the results found in our open trial (Kaye et al 1991), which suggests that fluoxetine administration is associated with a reduced rate of relapse in AN. Still, these data should be considered preliminary, as replication with larger sample sizes is needed. Finally, 64% of the subjects invited to participate in the study refused to do so. The high refusal rate is not surprising, since it is typical that people with AN are reluctant to take medication. However, this raises the question of the possibility of a different SSRI response in the group that refused fluoxetine.

In conclusion, this study offers preliminary evidence that fluoxetine may be useful in improving outcome and preventing relapse of patients with AN after weight restoration.

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