Fluoxetine After Weight Restoration in Anorexia Nervosa

A Randomized Controlled Trial

B. Timothy Walsh, MD
Allan S. Kaplan, MD, FRCPC
Evelyn Attia, MD
Marion Olmsted, PhD
Michael Parides, PhD
Jacqueline C. Carter, PhD
Kathleen M. Pike, PhD
Michael J. Devlin, MD
Blake Woodside, MD, FRCPC
Christina A. Roberto, BA
Wendi Rockert, MEd

Context Antidepressant medication is frequently prescribed for patients with anorexia nervosa.

Objective To determine whether fluoxetine can promote recovery and prolong time-to-relapse among patients with anorexia nervosa following weight restoration.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial. From January 2000 until May 2005, 93 patients with anorexia nervosa received intensive inpatient or day-program treatment at the New York State Psychiatric Institute or Toronto General Hospital. Participants regained weight to a minimum body mass index (calculated as weight in kilograms divided by the square of height in meters) of 19.0 and were then eligible to participate in the randomized phase of the trial.

Interventions Participants were randomly assigned to receive fluoxetine or placebo and were treated for up to 1 year as outpatients in double-blind fashion. All patients also received individual cognitive behavioral therapy.

Main Outcome Measures The primary outcome measures were time-to-relapse and the proportion of patients successfully completing 1 year of treatment.

Results Forty-nine patients were assigned to fluoxetine and 44 to placebo. Similar percentages of patients assigned to fluoxetine and to placebo maintained a body mass index of at least 18.5 and remained in the study for 52 weeks (fluoxetine, 26.5%; placebo, 31.5%; $P=.57$). In a Cox proportional hazards analysis, with prerandomization body mass index, site, and diagnostic subtype as covariates, there was no significant difference between fluoxetine and placebo in time-to-relapse (hazard ratio, 1.12; 95% CI, 0.65-2.01; $P=.64$).

Conclusions This study failed to demonstrate any benefit from fluoxetine in the treatment of patients with anorexia nervosa following weight restoration. Future efforts should focus on developing new models to understand the persistence of this illness and on exploring new psychological and pharmacological treatment approaches.

Trial Registration clinicaltrials.gov Identifier: NCT00288574

JAMA. 2006;295:2605-2612 www.jama.com

ANOREXIA NERVOSA IS A SERIOUS psychiatric illness with substantial morbidity and a lifetime mortality arguably as high as that associated with any psychiatric illness.[1] A major contributor to the poor prognosis of this illness is the high rate of relapse following initial treatment. Despite successful weight restoration, 30% to 50% of patients require rehospitalization within 1 year of discharge.[2,3] This discouraging experience has prompted interest in interventions aimed at preventing deterioration following weight restoration.

Patients with anorexia nervosa often exhibit symptoms of other psychiatric disorders,[4] such as depression and obsessive-compulsive disorder, which are responsive to antidepressant medication, suggesting that pharmacological interventions might be of use. Surprisingly, virtually all of the controlled trials of medication (most of which have been conducted during the initial phase of treatment when patients are underweight) have shown no benefit of medication compared with placebo.[5,6] Despite this lack of evidence of effectiveness, a substantial number of pa-

See also p 2659 and Patient Page.

Author Affiliations: New York State Psychiatric Institute/Columbia University Medical Center, New York, NY (Drs Walsh, Attia, Parides, Pike, and Devlin and Ms Roberto); and University of Toronto and Toronto General Hospital, Toronto, Ontario (Drs Kaplan, Olmsted, Carter, and Woodside and Ms Rockert).
Corresponding Author: B. Timothy Walsh, MD, Department of Psychiatry, College of Physicians and Surgeons of Columbia University/New York State Psychiatric Institute, 1051 Riverside Dr, Unit 98, New York, NY 10032 (btw1@columbia.edu).

tients with anorexia nervosa receive antidepressant medications. In our sites, approximately 60% of patients with anorexia nervosa seeking treatment report having been treated with a selective serotonin reuptake inhibitor (SSRI). Since the ineffectiveness of medication at low weight might be attributable to the effects of starvation, researchers have more recently explored the utility of medication after initial treatment has reversed the acute effects of starvation, with differing results.

In a retrospective case-control analysis, Strober et al[7] found no difference in the outcome of patients with anorexia nervosa taking fluoxetine following hospitalization compared with similar patients not taking fluoxetine. However, in a double-blind, placebo-controlled trial of 35 patients following significant weight restoration, Kaye et al[8] found fluoxetine to be superior to placebo in preventing relapse.

The primary aim of the current study was to determine, in a large sample, whether fluoxetine, compared with placebo, reduced the rate of relapse and enhanced psychological and behavioral recovery following initial treatment for anorexia nervosa. After successfully completing a course of intensive treatment aimed at weight restoration, patients were randomly assigned to receive fluoxetine or placebo and treated for up to 1 year in double-blind fashion. In addition to medication or placebo, patients received individual cognitive behavioral therapy specifically designed to prevent relapse.[9]

METHODS

Patient Recruitment

A patient was eligible to participate if she: (1) was a female between the ages of 16 and 45 years; (2) met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for anorexia nervosa (except the requirement for amenorrhea; women who meet all *DSM* criteria except amenorrhea do not appear to differ substantially from those meeting all criteria[10-12]) prior to the initial phase of treatment; (3) immediately prior to randomization, had successfully completed treatment at 1 of the study sites in an inpatient or day-program setting during which body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) reached at least 19 and was maintained for 2 weeks; (4) was not at imminent risk for suicide; (5) did not have a serious medical illness aside from the eating disorder; and (6) was medication free (with the exception of occasional lorazepam, 0.5 mg, or zopiclone, 7.5 mg, for anxiety or sleep disturbance).

Recruitment methods included word of mouth, referrals, the Internet, and advertisements. This study was described either during the first evaluation of patients considering admission to the eating disorders programs or following admission. However, formal recruitment and signing of the informed consent document did not occur until the end of the initial phase of treatment. The institutional review boards of the New York State Psychiatric Institute and Toronto General Hospital approved this study.

Treatment Prior to Randomization

The inpatient/intensive outpatient treatment at both sites focused on nutritional rehabilitation through the provision of supervised meals and behavioral and cognitive interventions. Both programs provided a weight maintenance period of several weeks following weight normalization, during which patients spent increasing amounts of time outside of the hospital.

Treatment

After signing consent, patients were randomly assigned to receive either fluoxetine or placebo. Randomization lists, stratified by site and binge-purge subtype, were generated by a computer program utilizing a random number generator seeded by time of day. Randomization assignments were kept in sealed envelopes and all clinical staff involved in the care of the patient, as well as study coordinators, remained blind to medication assignment during the study. Program staff not involved in the study prepared medication and placebo, which were contained in identical bottles. A statistician performed primary analyses while the research staff remained blind to medication assignment. To determine the effectiveness of blinding procedures, patients, physicians, and therapists were asked upon study termination to guess each patient's assignment. Psychiatrists (χ^2= 8.14, P=.004) and patients (χ^2=5.49, P=.02) guessed the correct medication assignment more frequently than chance, while therapists did not (χ^2=1.94, P=.16).

Medication was initiated in double-blind fashion 1 week prior to discharge from the hospital. The dose increased from 20 mg/d (1 pill) to 60 mg/d (3 pills) over 1 week under close supervision for any adverse effects. Medication dose was maintained at 60 mg/d unless there were adverse effects, in which case the dose was lowered at the discretion of the psychiatrist; if the patient's clinical status was deteriorating, the dose could be raised to a maximum of 80 mg/d (4 pills). After the first week receiving study medication, patients were discharged to outpatient care and treated for 12 months or until they met criteria for premature study withdrawal or voluntarily withdrew.

In addition to medication, all patients received a form of manualized cognitive behavioral therapy found to be useful in reducing relapse in anorexia nervosa.[9] Experienced psychologists and psychiatrists provided therapy, which consisted of 50 individual sessions of 45 minutes' duration. Patients were able to have up to 5 supplemental sessions with family members and/or significant others. A psychiatrist saw patients to monitor the dose of medication, adverse effects, and general medical status. Therapy sessions were audiotaped and reviewed by 2 of the authors (K.M.P. and M.J.D.) to assess treatment fidelity and adherence. Blood samples were obtained every 3 months for determination of plasma levels of fluoxetine and nor-fluoxetine.

Study participation was terminated and the patient was considered to have relapsed if (1) the participant's BMI fell

to or below 16.5 for 2 consecutive weeks; (2) severe medical complications (other than low weight) arose as a result of the eating disorder; (3) the participant was judged to be at imminent risk of suicide; or (4) the participant developed another severe psychiatric disorder requiring treatment. Thus, the definition of relapse captured severe worsening of symptoms of anorexia nervosa and/or the development of other major clinical problems.

Measures

To evaluate symptoms of disturbed eating behaviors and cognitions, depression, anxiety, and self-esteem, the following assessments were collected every 4 weeks: Eating Disorders Inventory (EDI),[13] the Beck Depression Inventory (BDI),[14] the Beck Anxiety Inventory (BAI),[15] and the Rosenberg Self-Esteem Scale (RSE).[16] Obsessions and quality of life were measured with the Yale Brown Cornell Obsessive Compulsive Scale for Eating Disorders (YBC-EDS)[17] and the Quality of Life Enjoyment and Satisfaction Questionnaire (QlesQ)[18] and were obtained before randomization, at 6 months, and again at study termination. Participants were weighed weekly.

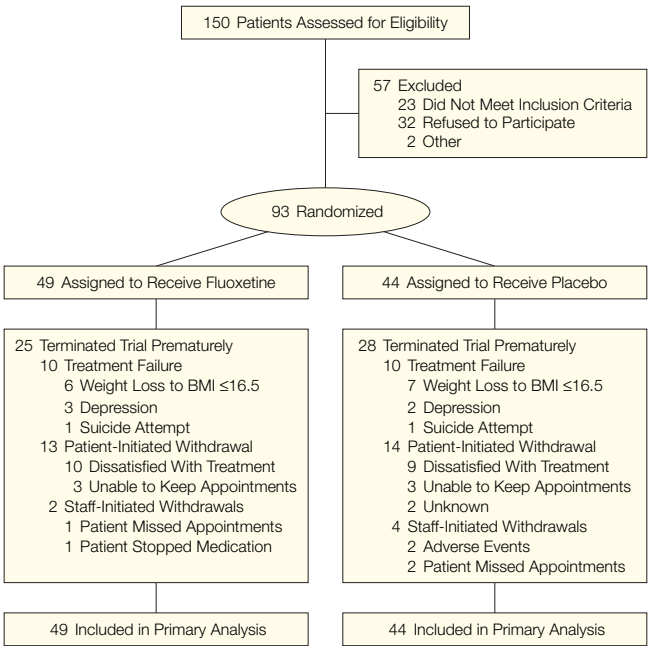
Statistical Methods

The study was designed to randomize 90 patients with equal allocation to fluoxetine and placebo. Ninety patients provide 90% power to detect a relative 50% reduction in relapse for fluoxetine compared with placebo based on a 2-sided .05 level log-rank test. A relapse rate of 70% was assumed for placebo and 35% for fluoxetine corresponding to a hazard ratio of approximately 0.34.

The primary outcome measure was time-to-relapse. Patients who voluntarily withdrew from treatment ("dropouts") were classified in 3 distinct ways. In the most conservative analysis, all patients who left the study prior to completing a full course of treatment (at least 38 psychotherapy sessions over 50 to 60 weeks) were considered to have relapsed. In a second least conservative analysis, only patients who met the predefined criteria described previously for study termination were considered to have relapsed; data from all other dropouts were censored. For the third analysis, dropouts were considered to have relapsed if they met any of the following criteria at the time they chose to end participation in the study: (1) had a BMI less than 17.5; (2) were binge eating and/or purging 2 or more times per week for the 4 weeks prior to dropping out; or (3) exhibited depressive and/or anxiety symptoms sufficient to interfere with functioning (eg, serious suicidal ideation). Cox proportional hazards regression was used to test for differences between randomization groups adjusting for site and diagnostic subtype (the 2 factors used to stratify the randomization) and by pretreatment BMI, which was found to differ significantly between randomization groups at the .05 level.

We also compared the proportion of patients in each group who failed to maintain normal weight (BMI≥18.5) for 52 weeks (ie, relapsed) using a χ^2 test. Patients whose weight fell below this level for 4 consecutive weeks or who withdrew from the study prior to 52 weeks were considered to have relapsed. Also, at study termination, patient status was classified according to modified Morgan-Russell criteria,[19,20] and the percentage of patients in fluoxetine and placebo groups classified as fair or better were compared using the χ^2 statistic. Additional secondary analyses examined differences between groups in change in symptoms over time using random-effects regression models. All outcome analyses adhered to the intention-to-treat principle; a *P* value of .05 using 2-sided tests was the criterion for significance for all analyses except the Cox proportional hazards regressions, for which, because of an interim analysis, a *P* value of .04 was used. Statistical analysis was completed using SAS version 9.1.3, SAS Institute Inc, Cary, NC, and SPSS version 13.0, SPSS Inc, Chicago, Ill.

Figure 1. Flow of Patients Through the Study



Body mass index (BMI calculated as weight in kilograms divided by height in meters squared).

RESULTS

Patient Characteristics

Patients were recruited between January 2000 and May 2004. The last patient completed the study in May 2005. One hundred fifty patients were evaluated for study participation (FIGURE 1).

Twenty-three did not meet criteria for eligibility, 32 declined participation, and 2 were excluded for other reasons. The remaining 93 patients entered the trial, 45 in New York, 48 in Toronto. Forty-nine patients were assigned to fluoxetine and 44 to placebo. On average, patients were a mean (SD) of 23 (4.6) years old, had been ill for 56.5 (44.7) months, had been previously hospitalized 2.1 (2.5) times, and had a BMI of 15.4 (1.8) at the time of entry into the initial phase of treatment. Forty-five patients (48.4%) met *DSM-IV* criteria for binge-purge subtype. There were no statistically significant differences in these parameters between the patients assigned to fluoxetine or placebo, or between the New York or Toronto sites.

At the time of randomization, patients in the fluoxetine and placebo groups were quite similar (TABLE 1). However, there was a small but statistically significant difference in BMI with patients receiving placebo starting the trial at higher BMI. Only patients who had gained to a BMI of at least 19 were eligible to enter the randomized phase of the study. In practice, most patients gained little additional weight, leading to very limited variance in BMI at the time of randomization. The limited variation contributed to the statis-

Table 1. Demographic Information, Body Mass Index, and Psychological Assessments at Prerandomization and at Study Termination

	Fluoxetine (n = 49)		Placebo (n = 44)	
	No.	Mean (SD)	No.	Mean (SD)
Subtype				
Restricting	25		23	
Binge/purge	24		21	
Age, y	49	22.4 (4.46)	44	24.2 (4.52)
Length of illness, y	43	4.05 (3.12)	38	4.92 (4.06)
Baseline				
Body mass index*	49	20.16 (0.48)†	44	20.45 (0.51)†
Rosenberg Self-Esteem Scale	49	22.94 (6.37)	43	23.12 (6.40)
Beck Depression Inventory	49	17.19 (11.21)	43	14.82 (10.66)
Beck Anxiety Inventory	49	16.27 (11.81)	41	14.96 (11.54)
Yale Brown Cornell Obsessive Compulsive Scale for Eating Disorders	48	15.41 (6.30)	43	13.09 (6.97)
Quality of Life Enjoyment and Satisfaction Questionnaire	48	49.63 (11.16)	44	52.07 (8.82)
Termination assessments				
Body mass index*	49	19.08 (2.1)	44	18.36 (1.6)
Rosenberg Self-Esteem Scale	43	23.77 (7.33)	41	22.71 (7.79)
Beck Depression Inventory	43	17.04 (13.38)	41	18.80 (13.53)
Beck Anxiety Inventory	43	9.07 (9.59)	42	10.74 (10.95)
Yale Brown Cornell Obsessive Compulsive Scale for Eating Disorders	39	13.40 (8.68)	41	13.90 (9.56)
Quality of Life Enjoyment and Satisfaction Questionnaire	43	51.70 (12.33)	40	52.15 (13.62)
Eating Disorder Inventory at preassessment				
Total score	49	72.69 (31.26)	44	71.00 (32.64)
Drive for thinness	49	12.62 (5.75)	44	11.70 (5.91)
Bulimia	49	1.64 (3.36)	44	2.00 (3.43)
Body dissatisfaction	49	17.22 (8.14)	44	18.73 (7.18)
Perfectionism	49	8.97 (4.46)	44	8.82 (4.62)
Ineffectiveness	48	11.40 (7.50)	44	10.61 (7.88)
Interpersonal distrust	49	5.91 (4.80)	44	4.75 (3.97)
Interoceptive awareness	49	9.95 (6.19)	44	9.97 (5.94)
Maturity fears	49	5.02 (6.22)	44	4.43 (5.12)
Eating Disorder Inventory at study termination				
Total score	43	60.93 (32.36)	42	65.29 (38.00)
Drive for thinness	43	10.56 (6.48)	42	11.63 (7.49)
Bulimia	43	2.84 (4.84)	42	2.48 (4.52)
Body dissatisfaction	43	13.37 (8.09)	42	14.98 (9.34)
Perfectionism	43	8.16 (4.67)	42	9.48 (4.88)
Ineffectiveness	43	9.77 (7.51)	42	11.27 (8.75)
Interpersonal distrust	43	5.35 (4.88)	42	4.56 (4.42)
Interoceptive awareness	43	7.16 (6.62)	42	7.35 (7.31)
Maturity fears	43	3.66 (4.73)	42	3.55 (4.20)

*Calculated as weight in kilograms divided by height in meters squared.
†Significant difference between fluoxetine and placebo groups ($t = 2.76$, $df = 91$, $P = .007$).

tical significance of the small difference in BMI between groups.

Outcome

Forty of the 93 patients completed the entire course of treatment and 53 terminated prematurely (Figure 1 and TABLE 2). The major reasons for premature termination were meeting a priori criteria for relapse and patient dissatisfaction with treatment. Patients were also withdrawn from the study if they failed to attend a minimum number of psychotherapy sessions in a quarter (12 during the first quarter, 9 during the second and third quarters, and 8 during the last quarter) or if they took less than 10 mg of the medication for 2 weeks or more. A 17-year-old patient assigned to fluoxetine made a suicide attempt during the study; there were no other unexpected adverse events. There were no significant differences between fluoxetine and placebo groups in BMI or in measures of psychological state at the time of termination (Table 1). There were no significant differences between the fluoxetine and placebo groups in the percentages of patients completing the full study (χ^2=0.001; P=.98), or in the average number of sessions of psychotherapy (fluoxetine, 38.1 [18.1]; placebo, 34.8 [16.8]; t=0.48; df=91; P=.63). However, there were significant differences in the rates of full-study completion between sites (New York, 28.9%; Toronto, 56.3%; χ^2= 7.094; P=.008) and between subtypes (binge-purge, 31.1%; restricting, 54.2%; χ^2=5.037; P=.03).

At the time of termination, similar percentages of patients in the fluoxetine and placebo groups met modified Morgan-Russell criteria for fair or better outcome (fluoxetine, 65.31%; placebo, 56.82%; χ^2=1.005; P=.32) (Table 2). By Morgan-Russell criteria at time of termination, there were no significant differences between sites or between binge-purge and restricting subtypes (data not shown).

Similar percentages of patients assigned to fluoxetine and to placebo maintained a BMI of at least 18.5 and remained in the study for 52 weeks (fluoxetine: 26.5%; placebo: 31.5%; χ^2=1.31, P=.57). A greater percentage of patients in Toronto (39.6%) met this outcome criterion compared with New York (17.8%; χ^2=5.36; P=.02). There was no statistically significant difference between binge-purge (22.2%) and restricting (35.4%) subtypes on this measure (χ^2=1.96; P=.16).

Table 2. Reason for Study Termination and Status at Termination as Per Modified Morgan-Russell Criteria for Outcome

	No. (%)		
	Fluoxetine (n = 49)	Placebo (n = 44)	Total (N = 93)
Reason for termination*			
Completed full study	21 (42.86)	19 (43.18)	40 (43.01)
Treatment failure†	10 (20.41)	10 (22.73)	20 (21.51)
Voluntarily withdrew	14 (28.57)	13 (29.55)	27 (29.03)
Withdrawn‡	4 (8.16)	2 (4.55)	6 (6.45)
Outcome status at termination			
Full recovery§	7 (14.29)	4 (9.09)	11 (11.83)
Good§	15 (30.61)	13 (29.55)	28 (30.11)
Fair§	10 (20.41)	8 (18.18)	18 (19.35)
Poor§	12 (24.49)	15 (34.09)	27 (29.03)
Other‖	5 (10.20)	4 (9.09)	9 (9.68)

*Proportion of patients completing full study with fluoxetine vs plabebo: χ^2 = 0.001, P = .98.
†Withdrawn because of worsening of anorexia nervosa and/or other significant clinical deterioration (see "Methods").
‡Withdrawn for nonadherence or potential drug adverse effects.
§Proportion of patients with outcome status of full recovery, good, or fair vs poor with fluoxetine vs placebo: χ^2 = 1.05, P = .32.
‖Dropped out early without meeting criteria for any of the other outcome categories.

Time-to-Relapse

The most conservative analysis of time-to-relapse, in which premature termination for any reason was considered to signify relapse, found no significant difference between the fluoxetine and placebo groups (β=–0.133; SE=0.288; df=1; P=.64) (FIGURE 2). At 52 weeks, 45% of the placebo group and 43% of the fluoxetine group had not relapsed. In this analysis, there were significant effects of site (β=0.814; SE=0.287; df=1; P=.005), of subtype (β=0.777; SE=0.285; df=1; P=.006), and of prerandomization BMI (β=–0.761; SE=0.323; df=1; P=.02). Patients in Toronto remained in the trial for a longer time prior to relapse than did those in New York, as did patients with the restricting subtype and patients with a higher BMI at prerandomization. Results from the analyses using the other methods of classifying dropouts were similar; neither indicated any difference between fluoxetine and placebo groups in time-to-relapse. At 52 weeks, using the least conservative analysis, in which patients who voluntarily withdrew were censored, 73% of the placebo group and 71% of the fluoxetine group had not relapsed. Using the analysis in which patients who dropped out were clinically classified, 51% of the placebo group and 49% of the fluoxetine group had not relapsed at 52 weeks.

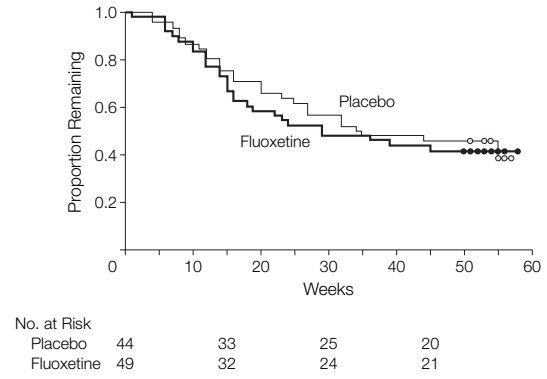
As noted previously, the average prerandomization BMI of the placebo group was slightly but significantly higher than that of the fluoxetine group. Because a higher BMI was associated with a longer time-to-relapse, BMI was included in the analyses described above to control statistically for the difference between fluoxetine and placebo groups. Additional secondary analyses of time-to-relapse were conducted including only the 55 patients whose prerandomization BMIs were greater than 20.15. Among these patients, there was no statistically significant difference between the mean prerandomization BMIs of the fluoxetine (n=24; 20.51 [0.42]) and placebo groups (n=31; 20.69 [0.41]; t(53) =1.61; P=.11). In none of these analyses did the difference between fluoxetine and placebo groups in time-to-relapse approach significance (P>.50 for all).

Because the study by Kaye et al[8] had excluded patients with binge eating, these analyses were repeated using data from only the 48 patients with the restricting subtype of anorexia nervosa. There was no evidence of a significant difference between the fluoxetine and placebo groups (data not shown).

Fluoxetine Levels

At the last visit, the mean (SD) dose of medication was 63.5 [15.8] mg/d for patients on fluoxetine and the equivalent of 71.4 [13.2] mg/d for patients receiving placebo ($t = 2.6$; $df = 91$; $P = .01$). Plasma samples for analysis of fluoxetine and nor-fluoxetine levels were available for 43 of the 49 patients assigned to receive fluoxetine. Plasma samples from 3 patients had no detectible fluoxetine or nor-fluoxetine. Exclusion of the data from these 3 patients did not substantially alter the results of the analyses of time-to-relapse. The average fluoxetine and nor-fluoxetine levels for the remaining 40 patients were 409 (225) and 297 (154) ng/mL, respectively; these levels are comparable with those reported in studies of obsessive-compulsive disorder[21] and the study by Kaye et al.[8] Among the patients with detectable fluoxetine or nor-fluoxetine levels, there was no significant relationship between the average total fluoxetine plus nor-fluoxetine plasma concentration and time-to-relapse using any of the methods for classifying dropouts (data not shown). Plasma samples were available for 38 of the 44 patients assigned to placebo; none had detectable levels of fluoxetine or nor-fluoxetine.

Figure 2. Patients Receiving Placebo and Fluoxetine Remaining in Treatment vs Number of Weeks After Treatment Inception



Circles indicate when patients left the trial after a full course of treatment (minimum 38 sessions, maximum 61 sessions over 12 months). Twelve month/full course of treatment criterion was satisfied if 38-session minimum was met between 50 and 60 weeks after randomization.

Table 3. Random-Effects Regression Analysis of Change During Treatment

	Random Effects Regression			
	Fluoxetine (SE)*	Placebo (SE)*	*Z* Score†	*P* Value‡
Weight, kg	–1.94 (0.51)	–2.14 (0.33)	0.32	.75
Beck Depression Inventory	0.12 (0.25)	0.20 (0.17)	0.27	.79
Beck Anxiety Inventory	–0.70 (0.12)	–0.22 (0.13)	2.69	.007
Rosenberg Self-Esteem Scale	0.12 (0.08)	0.07 (0.08)	0.40	.69
Quality of Life Enjoyment and Satisfaction Questionnaire[1]	0.23 (0.23)	0.31 (0.18)	0.28	.78
Eating Disorders Inventory				
Drive for thinness	–0.24 (0.09)	–0.081 (0.09)	1.31	.19
Bulimia	–0.11 (0.07)	0.035 (0.08)	0.74	.46
Body dissatisfaction	–0.24 (0.09)	–0.26 (0.09)	0.18	.86
Perfectionism	–0.037 (0.03)	0.05 (0.06)	1.14	.25
Yale Brown Cornell Obsessive Compulsive Scale for Eating Disorders	–0.18 (0.13)	0.028 (0.13)	1.13	.26

*Coefficients and standard errors indicate change per month.
†*Z* scores are for the difference between the coefficients for fluoxetine and placebo.
‡*P* values are for the difference between the coefficients for fluoxetine and placebo.

Prior SSRI Treatment

Twenty-four of the 93 patients had received 1 course of SSRI treatment (defined as 3 or more continuous weeks receiving an SSRI) prior to their participation in the current study, and 33 had received 2 or more previous courses of SSRI treatment. There were no significant differences between the fluoxetine and placebo groups in time-to-relapse using any of the criteria for classifying dropouts among patients with no prior SSRI treatment or among patients with no more than 1 course of prior treatment (data not shown).

Random-Effects Regression

Random-effects regression models were used to compare randomization groups over time using all available data from all patients (TABLE 3). The factors examined were weight, several measures of general (BDI, BAI, RSE) or specific (EDI-Drive for Thinness, Bulimia, Body Dissatisfaction and Perfectionism, and YBC-EDS) psychopathology, and a measure of quality of life (QlesQ). The only measure for which a significant fluoxetine-placebo difference was detected was the BAI; the mean (SD) change in BAI per month was –0.70 (0.12) in the fluoxetine group vs –0.22 (0.13) in the placebo group ($P = .007$; Bonferroni corrected: $P = .07$).

COMMENT

The current study was designed to determine whether the antidepressant medication fluoxetine reduced relapse following successful initial treatment of anorexia nervosa. Ninety-three patients entered the double-

blind phase, making this trial, to our knowledge, the largest controlled medication trial conducted to date in anorexia nervosa. All patients had reached a minimum BMI of 19.0, so that the acute effects of undernutrition were minimized. The average dose of fluoxetine was 63.5 mg/d similar to the dose routinely used in the treatment of bulimia nervosa. The study was conducted at 2 sites experienced in the treatment of anorexia nervosa, lending support to the generalizability of the findings. Despite these strengths, the current study found no convincing evidence that fluoxetine provided significant benefit compared to placebo. On virtually all measures, including time-to-relapse, rate of study completion, BMI, and clinical measures at time of termination, including depression, the group receiving fluoxetine was statistically indistinguishable from that receiving placebo. There was no indication that the effect of fluoxetine varied significantly by site, by subtype of anorexia nervosa, or by history of prior exposure to SSRIs. A single secondary analysis examining change in the BAI over time found a significant difference favoring the fluoxetine group; however, since the fluoxetine and placebo groups did not differ in similar analyses of 9 other measures, we cannot be confident that this difference between groups was not due to chance.

Both patients and their psychiatrists, but not their therapists, were more likely than chance to guess whether patients were receiving active medication. We speculate that this was due to the presence of minor adverse effects. However, since virtually no differences in outcome were detected between the fluoxetine and medication groups, it seems unlikely that this information substantially affected the assessment of clinical status.

The interpretation of treatment trials such as this one, in which a substantial number of patients did not complete the full course of treatment, can be problematic. However, since relapse soon after successful weight gain is a well-recognized clinical problem in the treatment of anorexia nervosa, we anticipated that many patients would not complete a full year of outpatient care and designed this study to examine the course of relapse during this time. The results of the survival analyses help clarify the reasons for premature termination and the impact of medication. Twenty of the 53 patients who did not complete a full course of treatment met our stringent, a priori criteria for full relapse and were therefore withdrawn from the study and referred for other treatment. An additional 24 of the 53 noncompleters had not deteriorated so severely as to require withdrawal but were clinically classified, blind to medication assignment, as doing sufficiently poorly to be considered as having relapsed at the time they left the study; many of these patients voluntarily withdrew from the study because of their lack of progress. Therefore, 44 (83%) of the 53 patients who did not complete treatment had deteriorated substantially, and this deterioration was a major contributor to their withdrawal. We had hoped that fluoxetine would alter the course of illness and thereby reduce such deterioration and the rate of withdrawal, as suggested by Kaye et al.[8] Unfortunately, medication assignment had no discernible impact on time-to-relapse whether all dropouts were considered to have relapsed, whether no dropouts were considered to have relapsed, or whether dropouts were classified as having relapsed based on their status at time of study termination. In other words, because discontinuation of treatment by patients with anorexia nervosa is a likely sign of impending relapse, systematic examination of such withdrawal can provide information about treatment efficacy. In this study, fluoxetine was no more efficacious than placebo.

A limitation on the conclusions of the current study is that we examined the utility of fluoxetine at a particular stage of illness and in conjunction with a particular form of structured psychological treatment. We cannot exclude the possibility that antidepressants might have an effect at other stages of illness, for example, in patients who have had anorexia nervosa for only a short time or who maintained a normal weight for a longer period of time before receiving antidepressant treatment. Similarly, it is conceivable that fluoxetine might provide benefit if it were the sole treatment provided or given in association with some other intervention. However, the results of the current study are consistent with most previous controlled trials of medication in anorexia nervosa, which have failed to show significant benefit from antidepressant medication compared with placebo.[5,22]

Unlike Kaye et al,[8] we were unable to demonstrate a difference between fluoxetine and placebo on time-to-relapse. A direct comparison between that study and the current one is confounded by a number of differences. In the current study, all patients received a structured psychotherapy specifically aimed to reduce relapse, whereas in the study by Kaye et al,[8] the psychosocial treatment received was not standardized; this difference may explain the high relapse rate in the placebo group in the study by Kaye et al.[8] In addition, criteria for relapse were less specific in that study and patients were encouraged to withdraw if they felt they were doing poorly. Because of limited information available about the treatment response of individuals with the restricting subtype of anorexia nervosa and of indications that such patients might respond more favorably to fluoxetine,[25] Kaye et al[8] focused their analysis on 35 patients who denied binge eating. Additional patients with binge eating were randomized according to personal communication with Walter H. Kaye, MD, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, and the restriction of the analysis to a subgroup may have inflated the possibility of a false-positive result.[27]

The current study has implications for both clinical practice and research. The present findings, coupled with those of previously published studies, indicate that the common practice of prescribing antidepressant medication is unlikely to provide substantial benefit for

most patients with anorexia nervosa, either when they are underweight or immediately upon weight restoration. These data imply that therapeutic efforts would be better devoted to psychological and behavioral interventions for which there is some, albeit modest, evidence of efficacy.[9,23] Future research on the utility of novel psychological treatments[24,25] and innovative psychotropic (eg, olanzapine)[26,27] and nonpsychotropic (eg, cycloserine)[28] medications is obviously needed. In addition, it may be important to examine the fundamental behavioral and cognitive disturbances of anorexia nervosa from fresh perspectives. Investigators have recently suggested that patients with anorexia nervosa might be viewed as having disturbances in extinguishing conditioned fears[29] or in changing cognitive set.[30,31] New frameworks for understanding the impressive persistence of anorexia nervosa may, eventually, lead to more effective treatments, which are sorely needed.

Author Contributions: Dr Walsh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Walsh, Kaplan, Attia, Olmsted, Parides, Carter, Pike, Devlin, Woodside, Rockert.
Acquisition of data: Walsh, Kaplan, Attia, Olmsted, Carter, Pike, Devlin, Woodside, Roberto, Rockert.
Analysis and interpretation of data: Walsh, Kaplan, Attia, Olmsted, Parides, Roberto, Rockert.
Drafting of the manuscript: Walsh, Kaplan, Parides, Roberto.
Critical revision of the manuscript for important intellectual content: Attia, Olmsted, Carter, Pike, Devlin, Woodside, Rockert.
Statistical analysis: Walsh, Parides, Roberto.
Obtained funding: Walsh, Kaplan.
Administrative, technical, or material support: Walsh, Kaplan, Attia, Olmsted, Roberto, Rockert.
Study supervision: Walsh, Kaplan, Pike.
Financial Disclosures: Dr Walsh has reported receiving research support from Eli Lilly and Co, Abbott Laboratories, Ortho-McNeil Pharmaceuticals, and GlaxoSmithKline. Drs Kaplan and Woodside have reported receiving research support from Eli Lilly and Co. Dr Devlin has reported receiving research support from Ortho-McNeil Pharmaceuticals and Eli Lilly and Co. Dr Attia has reported receiving research support from Eli Lilly and Co and Pfizer Inc. No other authors reported disclosures.
Funding/Support: This study was supported in part by grants MH060271 and MH60336 from National Institutes of Health. Eli Lilly supplied fluoxetine and placebo.
Role of the Sponsor: The National Institutes of Health and Eli Lilly had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.
Previous Presentation: Preliminary results of this study were presented at the meeting of the Eating Disorders Research Society; September 29, 2005; Toronto, Ontario.
Acknowledgment: We thank the staffs of the General Clinical Research Unit at New York State Psychiatric Institute/Columbia University Medical Center, New York, NY and of Toronto General Hospital, Toronto, Ontario. The members of the data and safety monitoring board: Sidney Kennedy, MD, University of Toronto, Toronto, Ontario; Andrew Leon, PhD, Weill Medical College of Cornell University, New York, NY; Steven Roose, MD, New York State Psychiatric Institute/Columbia University Medical Center; Jane Pearson, PhD, program officer, National Institute of Mental Health, Bethesda, Md. The members of the Eating Disorders Research Unit at New York State Psychiatric Institute/Columbia University Medical Center: Lauren Escott, MA, and Dana Satir, BA, Boston University, Boston, Mass, for data collection; Juli Goldfein, PhD, Diane Klein, MD, Lisa Kotler, MD, Laurel Mayer, MD, Pamela Raizman, PhD, Joanna Steinglass, MD, and Sara Wolk, PhD, New York State Psychiatric Institute/Columbia University Medical Center, for clinical care of study participants; Katharine Loeb, PhD, Mt Sinai School of Medicine, New York, NY; Sally Woodring, RN, New York State Psychiatric Institute/Columbia University Medical Center, for medication supply management; Jonathan Cohen, MS, New York State Psychiatric Institute/Columbia University Medical Center, for database creation and support. The members of the Toronto General Hospital research team: Traci McFarlane, PhD, and Randy Staab, MD, FRCP(C), Toronto General Hospital/University of Toronto; Pavla Reznicek, PhD, private practice, Toronto, for clinical care of study participants; Anita Federici, MSc, York University, Toronto, for data collection; and Nancy Lipson, MSW, RSW, Concurrent Disorders Service, Center for Addiction and Mental Health, Toronto, for medication supply management.

The following individuals included in the acknowledgments reported having received compensation from the NIH grant for their involvement in the study: Jonathan Cohen, MS; Lauren Escott, MA; Anita Federici, MSc; Juli Goldfein, PhD; Lisa Kotler, MD; Nancy Lipson, MSW; Pamela Raizman, PhD; Pavla Reznicek, PhD; Randy Staab, MD, FRCP(C); Dana Satir, BA; and Sara Wolk, PhD.

REFERENCES

1. Sullivan PF. Mortality in anorexia nervosa. *Am J Psychiatry*. 1995;152:1073-1074.
2. Pike KM. Long-term course of anorexia nervosa: response, relapse, remission, and recovery. *Clin Psychol Rev*. 1998;18:447-475.
3. Jones LM, Halford WK, Dooley RT. Long term outcome of anorexia nervosa. *Behav Change*. 1993;10:93-102.
4. Halmi KA, Eckert E, Marchi P, Sampugnaro V, Apple R, Cohen J. Comorbidity of psychiatric diagnoses in anorexia nervosa. *Arch Gen Psychiatry*. 1991;48:712-718.
5. Zhu AJ, Walsh BT. Pharmacologic treatment of eating disorders. *Can J Psychiatry*. 2002;47:227-234.
6. Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? *Am J Psychiatry*. 1998;155:548-551.
7. Strober M, Freeman R, DeAntonio M, Lampert C, Diamond J. Does adjunctive fluoxetine influence the post-hospital course of anorexia nervosa? a 24-month prospective, longitudinal followup and comparison with historical controls. *Psychopharmacol Bull*. 1997;33:425-431.
8. Kaye WH, Nagata T, Weltzin TE, et al. Double-blind placebo controlled administration of fluoxetine in restricting- and restricting-purging type anorexia nervosa. *Biol Psychiatry*. 2001;49:644-652.
9. Pike KM, Walsh BT, Vitousek K, Wilson GT, Bauer J. Cognitive behavior therapy in the posthospitalization treatment of anorexia nervosa. *Am J Psychiatry*. 2003;160:2046-2049.
10. Cachelin FM, Maher BA. Is amenorrhea a critical criterion for anorexia nervosa? *J Psychosom Res*. 1998;44:435-440.
11. Garfinkel PE, Lin E, Goering P, et al. Should amenorrhoea be necessary for the diagnosis of anorexia nervosa? evidence from a Canadian community sample. *Br J Psychiatry*. 1996;168:500-506.
12. Watson TL, Andersen AE. A critical examination of the amenorrhea and weight criteria for diagnosing anorexia nervosa. *Acta Psychiatr Scand*. 2003;108:175-182.
13. Garner DM, Olmsted MP. *The Eating Disorder Inventory Manual*. Odessa, Fla: Psychological Assessment Resources; 1984.
14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571.
15. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56:893-897.
16. Rosenberg M. *Conceiving the Self*. New York, NY: Basic Books; 1979.
17. Mazure CM, Halmi KA, Sunday SR, Romano SJ, Einhorn AM. The Yale-Brown-Cornell eating disorder scale: development, use, reliability and validity. *J Psychiatr Res*. 1994;28:425-445.
18. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of life enjoyment and satisfaction questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29:321-326.
19. Eckert ED, Halmi KA, Marchi P, Grove W, Crosby R. Ten-year follow-up of anorexia nervosa: clinical course and outcome. *Psychol Med*. 1995;25:143-156.
20. Russell GFM, Szmukler GI, Dare C, Eisler I. An evaluation of family therapy in anorexia nervosa and bulimia nervosa. *Arch Gen Psychiatry*. 1987;44:1047-1056.
21. Koran LM, Cain JW, Dominguez RA, Rush AJ, Thiemann S. Are fluoxetine plasma levels related to outcome in obsessive-compulsive disorder? *Am J Psychiatry*. 1996;153:1450-1454.
22. Holtkamp K, Konrad R, Kaiser N, et al. A retrospective study of SSRI treatment in adolescent anorexia nervosa: insufficient evidence for efficacy. *J Psychiatr Res*. 2005;39:303-310.
23. Lock J, le Grange D. Family-based treatment of eating disorders. *Int J Eat Disord*. 2005;37:S64-S67.
24. McIntosh VV, Jordan J, Carter FA, et al. Three psychotherapies for anorexia nervosa: a randomized, controlled trial. *Am J Psychiatry*. 2005;162:741-747.
25. Kaye WH, Weltzin TE, Hsu LK, Bulik CM. An open trial of fluoxetine in patients with anorexia nervosa. *J Clin Psychiatry*. 1991;11:464-471.
26. Powers PS, Santana CA, Bannon YS. Olanzapine in the treatment of anorexia nervosa: an open label trial. *Int J Eat Disord*. 2002;32:146-154.
27. Lagakos SW. The challenge of subgroup analyses–reporting without distorting. *N Engl J Med*. 2006;354:1667-1669.
28. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry*. 2004;61:1136-1144.
29. Strober M. Pathologic fear conditioning and anorexia nervosa: on the search for novel paradigms. *Int J Eat Disord*. 2004;35:504-508.
30. Tchanturia K, Morris RG, Surguladze S, Treasure J. An examination of perceptual and cognitive set shifting tasks in acute anorexia nervosa and following recovery. *Eat Weight Disord*. 2002;7:312-315.
31. Steinglass JE, Walsh BT, Stern Y. Set shifting deficit in anorexia nervosa. *J Int Neuropsychol Soc*. In press.

Financial Disclosures: None reported.
Funding/Support: No external funding was used for this study.
Previous Presentation: An abstract of this research was presented at the Fifth International Congress on Peer Review and Biomedical Publication; September 16-18, 2005; Chicago, Ill.
Acknowledgment: We thank Duncan Purvis, PhD, and Christine Wichems, PhD, employees of ProScribe Medical Communications, for their critical review of the manuscript, and John Wlodarczyk, PhD, for calculating the confidence intervals. Drs Purvis, Wichems, and Wlodarczyk received no financial compensation for their services.

1. Camacho LH, Bacik J, Cheung A, Spriggs DR. Presentation and subsequent publication rates of phase I oncology clinical trials. *Cancer*. 2005;104:1497-1504.
2. Wise P, Drury M. Pharmaceutical trials in general practice: the first 100 protocols: an audit by the clinical research ethics committee of the Royal College of General Practitioners. *BMJ*. 1996;313:1245-1248.
3. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication: ethical considerations in the conduct and reporting of research. http://www.icmje.org/index.html#ethic. Accessed November 1, 2005.
4. Wager E, Field EA, Grossman L. Good publication practice for pharmaceutical companies. *Curr Med Res Opin*. 2003;19:149-154.
5. Jacobs A, Wager E. European Medical Writers Association (EMWA) guidelines on the role of medical writers in developing peer-reviewed publications. *Curr Med Res Opin*. 2005;21:317-322.
6. Hamilton CW, Royer MG; AMWA 2002 Task Force on the Contributions of Medical Writers to Scientific Publications. AMWA position statement on the contributions of medical writers to scientific publications. *AMWA Journal*. 2003;18:13-16.
7. Flanagin A, Carey LA, Fontanarosa PB, et al. Prevalence of articles with honorary authors and ghost authors in peer-reviewed medical journals. *JAMA*. 1998; 280:222-224.
8. Phillips SG, Carey LA, Biedermann G. Attitudes toward writing and writing assistance in peer-reviewed articles. *AMWA Journal*. 2001;16:10-16.
9. Healy DT. Transparency and trust: figure for ghost written articles was misquoted [letter]. *BMJ*. 2004;329:1345.
10. Koreith K. Medical writing market appreciation. *The Centerwatch Monthly*. 2004;11:104. http://www.centerwatch.com/careers/CW1107_medicalwriting.pdf. Accessed May 9, 2006.
11. Hamilton CW, Mallia-Hughes M, Mitrany D, Foote MA. Comments on "The corporate author" [letter]. *J Gen Intern Med*. 2005;20:972.

CORRECTIONS

Incorrect Data: In the Original Contribution entitled "Fluoxetine After Weight Restoration in Anorexia Nervosa" published in the June 14, 2006, issue of *JAMA* (2006; 295:2605-2612), the boxes in Figure 1 that stated the reasons for premature termination for participants taking fluoxetine and placebo were switched. In the box describing reasons for termination for participants taking the placebo, "Suicide Attempt" was incorrectly substituted for "Clinical Deterioration." In Tables 1, 3, and the Measures section, The Yale Brown Cornell Obsessive Compulsive Scale for Eating Disorders should have been termed the Yale-Brown-Cornell Eating Disorder Scale and the Eating Disorders Inventory should have been termed the Eating Disorder Inventory. In the Table 2 footnotes, the χ^2 value after "§Proportion of patients with outcome status of full recovery, good, or fair vs poor with fluoxetine vs placebo" should have been $\chi^2=1.005$. In Table 3, the random-effects regression for the fluoxetine group for the Eating Disorder Inventory bulimia subscale should have been 0.11 rather than –0.11. In the last paragraph of the article, the references 24,25 after "psychological treatments" should have been numbered 24 and references 26,27 after "olanzapine" should have been numbered 26. None of these corrections affect the conclusions in the article.

Error in Wording: In the Editorial entitled "Radiosurgery and Whole-Brain Radiation Therapy for Brain Metastases: Either or Both as the Optimal Treatment" published in the June 7, 2006, issue of *JAMA* (2006;295:2535-2536), an error occurred in wording. In the final paragraph on page 2536, the term "stereotactic radiosurgery" should have been "whole-brain radiation therapy" in both instances. The sentence should have read "Aoyama et al[10] have prospectively shown that withholding whole-brain radiation therapy does not affect survival for patients who have 4 or fewer brain metastases; these patients have a higher rate of local brain failure, but apparently withholding whole-brain radiation therapy does not influence how patients die of their disease."

ity, specificity, positive predictive power, negative predictive power, and the C statistic) that we and others have used to compare mutation prediction models,[1,4] the ability to examine multiple predictors in logistic regression can add depth of understanding to statistical results. We agree that the corrective probability index we created was not based on a theory of inheritance but, rather, was a temporizing measure to improve the sensitivity of the model, hopefully to be replaced by a model wherein the parameters are adjusted for accuracy for single-case indicators in clinical settings such as ours. We intend to validate the effect of family structure in additional clinical and population-based data sets.

BRCAPRO certainly has great value in estimating the proportion of a population with a *BRCA* mutation and, in particular, in assigning likely carrier status when test results are uninformative. However, we maintain that from the clinician's perspective, neither BRCAPRO nor any of the other models tested is adequately accurate to determine whether to offer *BRCA* testing for a single case of breast cancer, especially in the setting of limited family structure.

While model-driven estimates have an important role as a component of the genetic cancer risk assessment process, we believe that the use of single point estimates as a threshold for recommending genetic testing should be discouraged in favor of a clinical judgment–grounded approach. This is consistent with the updated American Society of Clinical Oncology guidelines[5] and is critically important to individual women contemplating the benefits of risk reduction.

Jeffrey N. Weitzel, MD
jweitzel@coh.org
Veronica I. Lagos, MS
Deborah J. MacDonald, PhD
City of Hope
Duarte, California

Financial Disclosures: None reported.
Additional Contributions: Gwen Uman, PhD, Vital Research LLC, Los Angeles, California, provided assistance with the statistical methods. Dr Uman received compensation via a subcontract for her assistance.

1. James PA, Doherty R, Harris M, et al. Optimal selection of individuals for *BRCA* mutation testing. *J Clin Oncol*. 2006;24(4):707-715.
2. Domchek SM, Eisen A, Calzone K, Stopfer J, Blackwood A, Weber BL. Application of breast cancer risk prediction models in clinical practice. *J Clin Oncol*. 2003; 21(4):593-601.
3. Fewell Z, Smith GD, Sterne JA. The impact of residual and unmeasured confounding in epidemiological studies. *Am J Epidemiol*. 2007;166(6):646-655.
4. Berry DA, Iversen ES Jr, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of *BRCA1/BRCA2*, and prevalence of other breast cancer susceptibility genes. *J Clin Oncol*. 2002;20(11):2701-2712.
5. American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol*. 2003;21(12):2397-2406.

Table. BRCAPRO Prior Probability for Documented *BRCA* Carriers

Variable	BRCAPRO Prior Probability, No. (%)	
	<10%[a] (n = 16)[b]	≥10% (n = 13)
Ashkenazi Jewish ancestry		
Yes	0	8 (61.5)
No	16 (100)	5 (38.5)
Family structure		
Limited	11 (68.8)	10 (76.9)
Adequate	5 (31.2)	3 (23.1)

[a] A 10% probability threshold was chosen because it was the commonly accepted threshold at the time the study was conducted and has been used in other published studies.
[b] All 16 patients had a prior probability of less than 5%.

CORRECTION

Data Processing Error: In the Original Contribution entitled "Fluoxetine After Weight Restoration in Anorexia Nervosa: A Randomized Controlled Trial" published in the June 14, 2006, issue of *JAMA* (2006;295(22):2605-2612), a data processing error resulted in data errors in **Table 3**. The corrected analyses do not change the conclusions of the study. The data processing error also resulted in the reporting of a statistically significant difference between the New York and Toronto sites in the fraction of patients who remained in the study for 1 full year and whose body mass indexes (calculated as weight in kilograms divided by height in meters squared) did not fall to less than 18.5 for more than 4 weeks, which lost statistical significance (P=.10) in the corrected data set.

Table 3. Random-Effects Regression Analysis of Change During Treatment

	Random Effects Regression			
	Fluoxetine (SE)[a]	Placebo (SE)[a]	*Z* Score[b]	*P* Value[c]
Weight, kg	−2.11 (0.48)	−2.31 (0.32)	0.35	.73
Beck Depression Inventory	0.28 (0.28)	0.47 (0.20)	0.55	.58
Beck Anxiety Inventory	−0.72 (0.13)	−0.17 (0.14)	2.93	.003
Rosenberg Self-Esteem Scale	0.10 (0.07)	−0.06 (0.08)	1.53	.13
Quality of Life Enjoyment and Satisfaction Questionnaire	0.29 (0.24)	0.17 (0.20)	0.38	.70
Eating Disorder Inventory				
Drive for thinness	−0.24 (0.89)	−0.035 (0.70)	0.18	.86
Bulimia	0.15 (0.082)	0.12 (0.09)	0.25	.81
Body dissatisfaction	−0.22 (0.093)	−0.26 (0.095)	0.30	.76
Perfectionism	−0.059 (0.037)	0.052 (0.063)	1.52	.13
Yale-Brown-Cornell Eating Disorder Scale	−0.28 (0.13)	0.07 (0.12)	1.97	.05

[a] Coefficients and standard errors indicate change per month.
[b] *Z* scores are for the difference between the coefficients for fluoxetine and placebo.
[c] *P* values are for the difference between the coefficients for fluoxetine and placebo.

