Predictors of Treatment Acceptance and Completion in Anorexia Nervosa

Implications for Future Study Designs

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Context: There have been very few randomized controlled treatment studies of anorexia nervosa.

Objective: To evaluate factors leading to nonacceptance and noncompletion of treatment for 2 specific therapies and their combination in the treatment of anorexia nervosa.

Design: Randomized prospective study.

Setting: Weill-Cornell Medical Center, White Plains, NY; University of Minnesota, Minneapolis; and Stanford University, Stanford, Calif.

Patients: One hundred twenty-two patients meeting DSM-IV criteria for anorexia nervosa.

Interventions: Treatment with cognitive-behavioral therapy, fluoxetine hydrochloride, or their combination for 1 year.

Main Outcome Measures: Dropout rate and acceptance of treatment (defined as staying in treatment at least 5 weeks).

Results: Of the 122 randomized cases, 21 (17%) were withdrawn; the overall dropout rate was 46% (56/122) in the remaining patients. Treatment acceptance occurred in 89 (73%) of the 122 randomized cases. Of the 41 assigned to medication alone, acceptance occurred in 23 (56%). In the other 2 groups, acceptance rate was differentiated by high and low obsessive preoccupation scores (rates of 91% and 60%, respectively). The only predictor of treatment completion was high self-esteem, which was associated with a 51% rate of treatment acceptance.

Conclusion: Acceptance of treatment and relatively high dropout rates pose a major problem for research in the treatment of anorexia nervosa. Differing characteristics predict dropout rates and acceptance, which need to be carefully studied before comparative treatment trials are conducted.

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Anorexia nervosa is one of the most difficult psychiatric disorders to treat. Despite the refinement of treatment techniques, a recent review showed little convincing evidence of improved outcome of anorexia nervosa in the second half of the past century.1 There are few controlled treatment trials for this disorder because (1) the disorder is relatively rare, so that it is difficult to generate an adequate sample size in any one center; (2) patients with anorexia nervosa have a pronounced resistance to treatment and are at best ambivalent toward treatment; and (3) medical complications often require withdrawal from treatment protocols.

There are several possible explanations for these patients’ resistance to treatment compliance. One is that anorexia nervosa serves a strong positive function in the patient’s life, providing an escape from aversive developmental issues or distressing life events, often of an interpersonal nature. Thus, the disorder becomes highly reinforcing and the prospect of relinquishing the anorectic behavior pattern is terrifying to the patient. Another is the ego-syntonic nature of the disorder, which is demonstrated by the patient’s denial and refusal to accept the seriousness of the medical consequences of the disorder.2

These factors may account for the difficulty in recruiting sufficient numbers for treatment trials, in inducing compliance with treatments, and in retaining patients to the completion of treatment, producing less than convincing treatment comparisons. Unconvincing results may, in turn, further discourage an interest in participation in future clinical trials.

Of the 5 controlled studies with antidepressants, only 1 had a sample size of greater...
than 40 patients. Four of the 5 studies were conducted with inpatients in a structured environment. The single outpatient study was a relapse prevention study comparing fluoxetine hydrochloride with placebo. Ninety-five patients were invited to participate in this study and only 39 accepted, a drug refusal rate of 59%. In addition, the study reported a high dropout rate: 6 of 16 (38%) receiving fluoxetine and 16 of 19 (84%) receiving placebo.

Cognitive behavioral therapy (CBT) was developed to help anorectic patients examine and modify their negative thinking, dysfunctional assumptions, and overwhelming feelings of inadequacy. Two outpatient studies compared CBT with nutritional counseling. In one study, 25 patients were assigned to 20 sessions of CBT and 10 patients were assigned to nutritional therapy. All 10 in the latter group dropped out of treatment, compared with only 2 in the CBT group. In another study of relapse prevention, 33 patients were randomly assigned to 50 sessions of either individual CBT or nutritional counseling during a 12-month period. All patients who entered the study had achieved at least 90% of their target body weight and had maintained that for a minimum of 2 weeks in a structured inpatient setting before they entered the study. Relapse and dropout combined was significantly greater for nutritional counseling (73%) than for CBT (22%).

Substantial dropout rates pose a problem for clinical trials for several reasons. Analysis of completers may be biased, because the completers in one treatment group may not be comparable with those in another. The advantages of randomization may be lost when analysis focuses on completers. In any case, the sample size of completers is far less than the planned sample size and typically results in low power of statistical tests and poor precision in effect size estimators. When analysis is done by intention to treat, some imputation methods must be used for noncompleters, and the imputation methods may themselves mislead comparisons of treatments, because adequate imputation requires some understanding of the mechanisms leading to noncompletion in each treatment group. Such information is not readily available. Both to devise treatments that will be accepted by anorectic patients and to design clinical trials to evaluate the efficacy or effectiveness of those treatments, it is important to first understand the dropout phenomenon. Acceptance of treatment and staying in treatment for the minimum length of time to effect change are desirable for treatment utilization and evaluation to be meaningful.

Treatment utilization was found to be significantly related to severity of eating disorder symptoms, history of mood disorders, comorbid personality disorder, and overall functioning in a prospective longitudinal study. Thus, greater severity of eating disorder symptoms predicted greater utilization of treatment. It should be noted that showing up for treatment does not necessarily mean compliance with treatment or following treatment recommendations. The latter were not assessed in that study. A lifetime of history of mood disorders predicted greater utilization of individual psychotherapy. Presence of a personality disorder at intake was associated with greater subsequent treatment utilization for all forms of interventions. Worse functioning as assessed by the Global Assessment of Functioning was also associated with greater treatment utilization. This begins to suggest what factors might be important to consider in studying nonacceptance and noncompletion of treatments.

The major aim of this study was to evaluate treatment completion for 2 specific therapies and their use in combination in the treatment of patients with anorexia nervosa. No nontreatment control group was included because of ethical reasons. The focus of one therapy, CBT, was to change distorted beliefs about the patient’s weight and shape and to examine the function of the disorder in interpersonal terms to establish healthy eating behavior. The other treatment was a drug therapy with a selective serotonin reuptake inhibitor, which was expected to diminish the persistent preoccupations and rituals of patients with anorexia nervosa.

# METHODS

## SUBJECTS

All participating subjects met DSM-IV criteria for anorexia nervosa within 12 months before entering the study. Diagnoses were established by the Structured Clinical Interview for DSM-III-R. All patients had signed an institutional review board–approved consent form. Patients between the ages of 14 and 50 years were accepted into the study. The SCID-P and SCID-2 structured interviews were conducted by trained psychologists or psychiatrists who had previously established an acceptable diagnostic reliability. Patients had to be within 73% of a target weight established by the National Center for Health Statistics growth curves for children or the 1959 Metropolitan Life Insurance Co height-weight charts, which highly correlate with the Frisch menstrual cycle weight charts.

Patients meeting study criteria from 3 centers (Weill-Cornell Medical Center, White Plains, NY; University of Minnesota, Minneapolis; and Stanford University, Stanford, Calif) were randomly assigned with equal probability within each center to 3 treatments. All participants received medical management. In addition, 1 group received CBT; the second, CBT and the selective serotonin reuptake inhibitor fluoxetine; and the third, fluoxetine alone.

## TREATMENT DESIGN

Treatment occurred during a 1-year period. The CBT sessions were scheduled twice per week for the first month, once per week for months 2 to 6, twice per month for months 7 to 9, and once per month for months 10 to 12. This gave a total of 37 manualized CBT sessions conducted by experienced PhD-level therapists. The CBT was a manual-based intervention developed for this protocol.

Medical management sessions were conducted by a psychiatrist after the therapy session weekly for the first month. The sessions then occurred twice a month through the fourth month and then monthly. The total number of medical management sessions was 18. Those sessions lasted approximately 15 minutes.

For patients who received fluoxetine, the drug was administered during the medical management session. Patients were brought to the maximum dose of medication (60 mg) within 6 weeks. At the end of 6 weeks they continued taking the maximum dose they could tolerate. Figure 1 depicts the overall design and the numbers screened, interviewed, and randomized, with dropout and withdrawal rates by site and by treatment group.

*Figure 1*
STATISTICAL METHODS

Baseline characteristics were compared by means of a 2-way design with site, treatment, and their interaction as the independent measures. To avoid the false-positive results associated with multiple testing, a 1% significance level was used for baseline comparisons between the sites and treatment groups. The Cox proportional hazards regression model was used to analyze center and treatment effects on dropout rates. Recursive partitioning based on signal detection according to Kraemer,12 in which equal clinical emphasis was placed on false-positive and false-negative results, using a stopping rule with \( P < .01 \), was used to determine algorithms based on baseline data to predict subjects who were likely either not to accept treatment or not to complete treatment. Kaplan-Meier survival curves were computed to illustrate the results of these analyses.

Cutoff points for obsessive preoccupations and self-esteem were calculated by the signal detection program, which considers each value and determines the most efficient cutoff point. There were 22 variables used in the signal detection analyses: the site center; the treatment type; clusters A, B, and C; personality disorders; history of obsessive-compulsive disorder; previous hospitalization; previous outpatient treatment; history of depression; baseline body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters); age; education; personality disorder; purging behavior; depression (Beck Depression Inventory); Rosenberg Self-esteem Scale; Multidimensional Personality Questionnaire (impulsivity subscale); Social Adjustment Scale; Yale-Brown Obsessive-Compulsive Scale; Eating Disorder Examination scores (preoccupation, ritual, and motivation for change subscales); and global Eating Disorder Examination scores.

RESULTS

The Table presents the demographic and clinical descriptors of the patients participating in this study by site. The overall mean BMI of 17.8 for patients entering this study is below the normal weight range (BMI of 19–25). The median BMI for the patients was 17.5. Eighty-nine percent of the patients participating in the study were older than 18 years; because anorectic patients are resistant and unwilling to enter treatment, there is often poor cooperation with treatment in patients 18 years old and older because they are of legal age and parental pressure to comply with treatment may be eased.

About a third of the participating patients had previous hospitalizations and two thirds had previous outpatient treatment, which indicates that this was a fairly severely ill group. The comorbidity of depression, obsessive-compulsive disorder, and personality disorders was comparable with findings in previous studies. More than half of the patients engaged in purging, which has been a poor prognostic indicator in previous studies.1

No statistically significant \( (P < .01) \) site differences were found.

DROP OUTS AND WITHDRAWALS

A total of 21 participants (17%) were withdrawn from the study. The main reason for withdrawal was treatment failure as defined previously (17 [81%]). Other reasons included pregnancy (n = 2) and intolerable side effects of medication (n = 3). Among the 101 remaining patients, the dropout rate was substantial: 55% (56/101), or an overall compulsive behavior, the Social Adjustment Scale,14 the Multidimensional Personality Questionnaire (impulsivity subscale only),15 and the Beck Depression Inventory.16

For the core eating disorder psychopathology, patients received the following assessments: the Eating Disorder Examination,11 a semistructured interview for assessment of specific psychopathology of eating disorders; the Three Factor Eating Questionnaire (Disinhibition Scale only)16; weight, measured during the evaluation week and at the beginning of every treatment session; Side Effects Inventory, an observer rating form developed by the Psychopharmacology Branch of the National Institute of Mental Health that covers a comprehensive range of side effects often present with psychotherapeutic drugs16; the Yale-Brown-Cornell Eating Disorder Scale, a semistructured interview similar in design to the Yale-Brown Obsessive-Compulsive Scale that measures symptom severity typical of eating disorder preoccupations and rituals;16 and the Rosenberg Self-esteem Scale.17 Major assessment batteries were administered at baseline and weeks 24, 36, and 52.

At the initial evaluation, patients had a complete blood cell count and measurement of serum electrolytes with phosphorus. This was repeated at the end of 3 months of treatment and whenever medically indicated.

Patients were withdrawn from the study if they dropped below 70% of their target weight at any time during the study or if they experienced medical difficulties. Medical difficulties were defined as severe electrolyte disturbance that required hospitalization, severe depression that required additional treatment, or the development of any severe medical complications necessitating intensive medical intervention (eg, cardiac arrhythmia or significant liver dysfunction).
rate of 46% (56/122). The main reason reported for dropout was dissatisfaction with some aspect of the treatment (68% [38/56]). An additional 11 participants (20%) dropped out very early in treatment, 4 individuals (7%) were withdrawn by their families, and 2 individuals (4%) dropped out later in treatment, all without indicating a reason.

Figure 2 shows the survival curve to noncompletion of the study for the 3 treatment groups, resulting from either withdrawal or dropout. There was substantial attrition in all groups within the first 5 weeks. Consequently, we defined “treatment acceptors” as those who had at least 5 weeks of treatment, and “treatment completers” as those who completed the 1-year program. Our analyses did not allow us to differentiate predictors for withdrawals and dropouts.

**TREATMENT ACCEPTANCE**

Of the 122 randomized patients, 89 (73%) accepted treatment. The strongest predictor of acceptance, according to signal detection analysis, was treatment type, distinguishing between medication (with acceptance in 23 of 41 patients [56%]) and the other 2 treatments (with acceptance in 66 of 81 patients [81%]). This latter group was further divided into those with a low score for preoccupation (H.11021/8) on the Yale-Brown-Cornell Eating Disorder Scale, who had an acceptance rate of 52% (13 of 25 patients), and those with higher preoccupation (score H.11350/8), who had an acceptance rate of 91% (51 of 56 patients). Thus, 3 distinct subgroups of participants emerged: 1 comprising those assigned to medication, in which the acceptance rate was 56%; 1 including those assigned to the other 2 treatments who had preoccupation scores less than 8 (acceptance rate, 52%); and 1 consisting of those assigned to the other 2 treatments who had preoccupation scores of 8 or more (acceptance rate, 91.1%). Survival curves for these 3 groups during the first 5 weeks are shown in Figure 3.
TREATMENT COMPLETION

Eighty-nine of the original 122 participants were treatment acceptors. Of these, 45 (51%) completed treatment, or 37% (45/122) of all who were randomly assigned. The one and only predictor of treatment completion in a signal detection analysis was self-esteem. A low self-esteem (Rosenberg Self-esteem Scale score ≥23) led to a 40% completion rate (27 of 68 patients), whereas a high self-esteem (score <23) was associated with an 86% completion rate (18 of 21 patients). Type of treatment was not a significant predictor of treatment completion among the treatment acceptors. Figure 4 shows the survival curves among the treatment acceptors starting at 5 weeks to the end of treatment for those in the 2 self-esteem groups.

COMMENT

Among the strengths of this study is the relatively large sample recruited from 3 centers across the United States. The major assessments were interview based, and the assessors were all experienced and had high agreement rates. Cognitive-behavioral therapy was carried out by experienced therapists following a manual, with centralized training and refresher sessions and detailed on-site supervision. Medication treatment was carried out by psychiatrists experienced in treating anorexia nervosa. Nevertheless, only 27% of those randomized to medication completed treatment, compared with 43% in the CBT group and 38% in the combination group. This compromises any attempt to evaluate the relative effectiveness of these treatments.

The very low rate of acceptance in the medication treatment group does not seem to pertain when medication is given together with some form of psychotherapy. The poor acceptance of medication in anorexia treatment studies was also demonstrated by Kaye et al. In this study, 95 anorectic patients were invited to participate and only 39 accepted, giving a drug refusal rate of 39%. This would begin to suggest that medication alone cannot be an effective treatment for anorexia, if only because the majority of anorectic patients will not accept such treatment.

Even for treatments involving psychotherapy, acceptance of treatment and relatively high dropout rates pose a major problem for research in the treatment of anorexia nervosa, limiting the sample size and reducing the power in intent-to-treat analyses and, in addition, introducing bias in completer analyses. As we have shown, it is likely that differing characteristics (in this study, obsessive preoccupation and self-esteem at baseline) predict different dropout rates. It is necessary, therefore, to first deal with the acceptance and dropout problems before conducting trials with different treatments.

Some clues as to how to remediate this problem emerge from this study, although further research is needed. While it was clear initially that a no-treatment group is not viable within the structure of a randomized clinical trial of patients with chronic anorexia, it is now also clear that medication alone is not a viable treatment. At one site, for example, 165 patients were screened, 16 were randomized to medication, and only 1 completed that treatment. Furthermore, one major reason for dropout from such trials is medical difficulties. Therefore, it is necessary to develop treatment protocols that include dealing with such medical difficulties without dropping patients from the protocol to which they have been assigned. It is of interest that the median BMI of this patient treatment sample was 17.5. This means that many of the patients participating in this study partially restored their target rate. It is possible that recruitment and retention in randomized controlled treatment studies may be even worse with anorectic patients who have not partially restored their target rate.

Finally, in the groups involving psychotherapy, patients with high obsessive preoccupation tended to have relatively high acceptance rates for treatments involving psychotherapy. Among the acceptors, those with high self-esteem were more likely than those with low self-esteem to complete treatment. It is possible that devising different treatment protocols for other patients with anorexia nervosa that take into consideration such baseline characteristics might begin to alleviate the dual problems of treatment acceptance and dropout. For example, remedies need to be identified to improve acceptance of treatment and reduce dropout in those patients with low obsessive preoccupation and low self-esteem. Further research along these lines is clearly needed.

The difficulty both in treating patients with chronic anorexia shown in this and previous studies and in the consequent difficulty in evaluating the effectiveness of treatments in randomized clinical trials leads inexorably to the conclusion that prevention of chronicity, with its associated high morbidity and mortality, should be a major aim. This would mean focusing on early diagnosis and adequate treatment of the younger anorectic patient. However, until such time that chronic anorexia can be prevented, the improvement of outpatient treatments for patients with chronic anorexia is made more urgent by the limitations imposed on the duration of hos-
hospital stays for such patients in the era of managed care, and evaluation of such treatments facilitated by consideration of the reasons for noncompletion of treatments. On the basis of the outcome of this trial, and other similar trials already reported, it appears premature to conduct randomized controlled trials for adults with anorexia nervosa, until the reasons for poor acceptance and high dropout rates from randomized controlled trials have been identified and methods to remediate these serious problems have been devised.

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REFERENCES


