

# Anorexia Nervosa Treatment: A Systematic Review of Randomized Controlled Trials

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## ABSTRACT

**Objective:** The RTI International-University of North Carolina at Chapel Hill Evidence-based Practice Center (RTI-UNC EPC) systematically reviewed evidence on efficacy of treatment for anorexia nervosa (AN), harms associated with treatments, factors associated with treatment efficacy, and differential outcome by sociodemographic characteristics.

**Method:** We searched six major databases for studies on the treatment of AN from 1980 to September 2005, in all languages against *a priori* inclusion/exclusion criteria focusing on eating, psychiatric or psychological, or biomarker outcomes.

**Results:** Thirty-two treatment studies involved only medications, only behavioral interventions, and medication plus behavioral interventions for adults or adolescents. The literature on medication treatments and behavioral treatments for adults with AN is sparse and inconclusive. Cognitive behavioral therapy may reduce relapse risk for adults with AN af-

ter weight restoration, although its efficacy in the underweight state remains unknown. Variants of family therapy are efficacious in adolescents, but not in adults.

**Conclusion:** Evidence for AN treatment is weak; evidence for treatment-related harms and factors associated with efficacy of treatment are weak; and evidence for differential outcome by sociodemographic factors is nonexistent. Attention to sample size and statistical power, standardization of outcome measures, retention of patients in clinical trials, and developmental differences in treatment appropriateness and outcome is required. © 2007 by Wiley Periodicals, Inc.

**Keywords:** anorexia nervosa; clinical trials; evidence-based review; eating disorders; cognitive behavioral therapy; antidepressants; family therapy

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## Introduction

Given the high morbidity and mortality associated with anorexia nervosa (AN), developing effective treatments is critical. A workshop sponsored by the

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National Institute of Mental Health (NIMH) examined problems in conducting research on AN treatment.<sup>1</sup> It highlighted obstacles such as relatively low incidence and prevalence, lack of consensus on best treatments, variable presentation within the patient population based on age and illness factors, high costs of providing treatment, and the complex interaction of medical and psychiatric problems associated with illness.

To explore these issues further, the Agency for Healthcare Research and Policy (AHRQ), on behalf of the National Institutes of Health (NIH) Office of Research on Women's Health, the NIMH, and the Health Resources and Services Administration, commissioned the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) to conduct an extensive systematic review of the literature on treatment and outcomes of AN, bulimia nervosa, and binge eating disorder.<sup>2</sup> We present here results of this review of randomized controlled trials (RCTs) for AN, comment on the quality and strength of the evidence, highlight continuing gaps and deficiencies in the evidence

**TABLE 1. Criteria for searches on treatment of AN**

Category	Criteria
Study population	Humans All races, ethnicities, and cultural groups 10 years of age or older
Study settings and geography	All nations
Time period	Published from 1980 through September 2005
Publication criteria	Included: • All languages • Articles in print Excluded: • Articles in gray literature or nonpeer-reviewed journals or unobtainable during the review period
Admissible evidence (study design and other criteria)	Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results AN must be diagnosed according to DSM III, DSM III-R, DSM IV, ICD-10, Feighner, or Russell criteria Eligible study designs include randomized controlled trials (RCTs): Double-blinded, single-blinded, and cross-over designs (we report data for the portion of the trial completed before the first cross-over) Initiated with 10 or more participants and followed for any length of time

base, and offer recommendations for future research.

To plan the systematic review and provide ongoing consultation, we solicited input from a technical expert panel (TEP) of 10 individuals (researchers, practitioners, and a patient advocate). On the basis of AHRQ's initial commission and the TEP's comments, we constructed key questions to guide this review:

1. What is the evidence for the efficacy of treatments or combinations of treatments for AN?
2. What is the evidence of harms associated with the treatment or combination of treatments for AN?
3. What factors are associated with efficacy of treatment among patients with AN?
4. Does the efficacy of treatment for AN differ by sex, gender, age, race, ethnicity, or cultural group?

## Method

### *Inclusion and Exclusion Criteria*

Our *a priori* inclusion and exclusion criteria (Table 1) were broad but excluded data that combined eating disorders, because we could then not separately examine AN outcomes. Outcome categories included eating, psychiatric and psychological, and biomarker measures.

### *Literature Search and Retrieval Process*

**Databases and Search Terms.** We searched six databases: MEDLINE<sup>®</sup>, the Cumulative Index to Nursing and

Applied Health, PsycINFO, the Educational Resources Information Center (ERIC), the National AGRICultural OnLine Access, and Cochrane Collaboration libraries. We generated a list of Medical Subject Heading (MeSH) search terms for MEDLINE searches and used comparable terms for other databases. MeSH terms included anorexia and AN. We limited our searches by type of study, including RCT, single-blind method, double-blind, and cross-over designs. We also solicited articles from experts in the field, including the TEP and peer reviewers of the draft report.

**Article Selection and Review.** We reviewed each abstract systematically against *a priori* criteria to determine inclusion. A first reviewer evaluated abstracts for inclusion. If that reviewer judged the article to be appropriate for inclusion, it was retained. Articles that the reviewer determined did not meet our criteria were re-evaluated by a senior reviewer who could reverse the decision. Reasons were assigned to each exclusion.

### *Evaluation of Quality and Strength of Evidence*

**Rating the Quality of Individual Articles.** Based on criteria adapted from West et al.,<sup>3</sup> we graded each study according to 25 items in 11 categories: (1) research aim/study question, (2) study population, (3) randomization, (4) blinding, (5) interventions, (6) outcomes, (7) statistical analysis, (8) results, (9) discussion, (10) external validity, and (11) funding/ sponsorship.

We weighted each item equally and calculated a score out of 100%, excluding items not applicable based on study design. We collapsed scores into three categories: poor (0–59%); fair (60–74%); and good (75–100%). Quality grades were the averaged ratings of two independent reviewers, and we attempted to reconcile grades if scores differed by 20 points or more. Our rating scale is

**TABLE 2. Criteria to rate strength of evidence on treatment of AN**

Strength of Evidence	Criteria
Strong	The evidence is from studies of strong design; results are both clinically important and consistent, with minor exceptions at most; results are free from serious doubts about generalizability, bias, or flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power
Moderately strong (moderate)	The evidence is from studies of strong design, but some uncertainty remains because of inconsistencies or concern about generalizability, bias, research design flaws, or adequate sample size. Alternatively, the evidence is consistent but derives from studies of weaker design
Weak	The evidence is from a limited number of studies of weaker design. Studies with strong design either have not been done or are inconclusive
None/nonexistent	No evidence base. No published literature

based on the best available approaches, but it should be interpreted with caution because it has not been validated.

**Rating the Strength of the Available Evidence.** We evaluated the quality of the literature as a whole based on the criteria developed by Greer et al.<sup>4</sup> The approach includes three domains: quality of the research, quantity of studies (including number of studies and adequacy of the sample size), and consistency of findings. It yields four categories (strong, moderately strong, weak, and nonexistent) (Table 2). We rated quality for each key question separately.

## Results

We identified 32 studies published in 35 articles addressing treatment efficacy for AN. Weight gain is the primary outcome variable in treating AN patients. Secondary outcomes include reducing the psychological features of AN (e.g., body dissatisfaction and drive for thinness); decreasing associated behaviors such as overexercising, resuming menses; and, in the bingeing and purging subtype, reducing those behaviors. Additional psychiatric outcomes include lessening depression and anxiety.

We do not discuss here 13 studies with a quality rating of "poor."<sup>5–17</sup> The most frequent deficiencies contributing to a poor rating included: a fatal flaw in or failure to describe randomization procedures; absence or failure to report blinding; failure to report adverse events; absence of power analyses; lack of controls for confounding; absence of an intention-to-treat approach; and failure to report funding sources.

### Medication Trials for AN

We rated two medication trials as good<sup>18,19</sup> and six as fair<sup>20–25</sup> (Table 3). The medications studied included second-generation antidepressants,<sup>18,20</sup>

tricyclic antidepressants,<sup>21,22</sup> hormones,<sup>19,23,24</sup> and nutritional supplements.<sup>25</sup>

Medication trials were commonly conducted in the context of clinical management or during or following inpatient refeeding. No study reported race or ethnicity of participants; all but one reported sex of participants. Only one study explicitly reported intention-to-treat analyses.<sup>19</sup> Participants numbered from 15 to 72 (average across studies, 23 participants); total enrollment across trials was 345. Based on those studies that reported sex, the study population included 319 women and 1 man.

**Fluoxetine.** Two trials used fluoxetine at different stages of refeeding. One inpatient study randomized 31 women (aged 16–45 years) who had achieved weight restoration of at least 65% of ideal body weight (IBW) to fluoxetine (60 mg/day) or placebo.<sup>18</sup> Mean body mass index (BMI) at randomization was 15 kg/m<sup>2</sup>. Patients continued to receive psychotherapy. No significant differences emerged between fluoxetine and placebo on weight gain (16 versus 13 pounds), psychological features of eating disorders, or depression or anxiety measures. Three percent of participants dropped out of fluoxetine treatment.

In another study, patients were randomly assigned to either fluoxetine or placebo before inpatient discharge, with a beginning dosage of 20 mg/day adjusted over 52 weeks to a maximum of 60 mg/day.<sup>20</sup> The range of weight for all participants at randomization was 76–100% average body weight (ABW), with the majority above 90%. Outpatient psychotherapy was permitted. At endpoint, patients on medication did not differ significantly from those on placebo on eating, psychological, or biomarker measures. Dropout was considerable. Of 39 individuals randomized, only 13 remained at the 52-week endpoint representing a 47% dropout from fluoxetine and 85% dropout from placebo.

**Tricyclic Antidepressants.** Halmi et al.<sup>21</sup> compared amitriptyline (160 mg/day), cyproheptadine (32 mg/

**TABLE 3. Results from medication trials for AN**

Source, Treatment, Sample Size, Quality Score	Study Location and Setting, Percentage Female, Age	Significant Differences Between Groups
Attia et al., <sup>18</sup> fluoxetine vs. placebo, enrolled: 33, dropouts: 3%, good	US: inpatient; female: 100%; age range: 16–45	<b>At endpoint:</b> not reported <b>Change over time:</b> none
Kaye et al., <sup>20</sup> fluoxetine vs. placebo, enrolled: 39, dropouts: 66%, fair	US: inpatient and outpatient; female: 100%; age, mean (SD)—fluoxetine: 23 (9), placebo: 22 (6)	<b>At endpoint:</b> none <b>Change over time:</b> none
Halmi et al., <sup>21</sup> amitriptyline vs. cyproheptadine vs. placebo, enrolled: 72, dropouts: 25%, fair	US: inpatient; females: 100%; age range: 13–36	<b>At endpoint:</b> cyproheptadine associated with fewer days to target weight, higher caloric intake, and less depressed mood than placebo <b>BN subgroup:</b> amitriptyline associated with improved treatment efficacy compared to cyproheptadine. Neither differed from placebo <b>Non-BN subgroup:</b> cyproheptadine associated with improved treatment efficacy compared with placebo. No other comparisons were significant <b>Change over time:</b> not reported
Biederman et al., <sup>22</sup> amitriptyline vs. placebo, enrolled: 25, dropouts: 0%, fair	US: inpatient and outpatient; female: not reported; age range: 11–27	<b>At endpoint:</b> none <b>Change over time:</b> not reported
Miller et al., <sup>24</sup> testosterone vs. placebo, enrolled: 38, dropouts: 13%, fair	US: outpatient; female: 100%; age range: 18–37	<b>At endpoint:</b> testosterone associated with less depressed mood <b>Change over time:</b> depressed mood increased less in testosterone-treated group
Hill et al., <sup>19</sup> growth hormone ( <i>rhGH</i> ) vs. placebo, enrolled: 15, dropouts: 0%, good	US: inpatient; female: 93%; age range: 12–18	<b>At endpoint:</b> <i>rhGH</i> associated with fewer days to restoration of normal orthostatic response compared with placebo <b>Change over time:</b> not reported
Klibanski et al., <sup>23</sup> estrogen/progestin vs. nonmedication control, enrolled: 48, dropouts: 8%, fair	US: outpatient; female: 100%; age range: 16–43	<b>At endpoint:</b> none <b>Change over time:</b> none
Birmingham et al., <sup>25</sup> zinc vs. placebo, enrolled: 54, dropouts: 35%, fair	Canada: inpatient; female: 100%; age range: 15 and older; zinc, mean (SD): 20.6 (3.8); placebo, mean (SD): 23.8 (6.1)	<b>At endpoint:</b> none <b>Change over time:</b> zinc superior in rate of body mass index increase

Notes: BN, bulimia nervosa; SD, standard deviation; US, United States.

day), and placebo in 72 women aged 13–36 years. Daily caloric intake was significantly higher for cyproheptadine than for placebo; significantly fewer days were needed to achieve target weight (in those who did) with both amitriptyline and cyproheptadine groups than with placebo. Attrition was moderately high: amitriptyline group, 30%; cyproheptadine group, 25%; and placebo group, 20%. In another study, amitriptyline in doses up to 175 mg/day in 25 youth (aged 11–17 years) led to no significant differences in eating, mood, or weight outcomes in comparison with placebo.<sup>22</sup> No patients dropped out in this trial.

**Hormones.** Miller et al. investigated 3 weeks of transdermal testosterone (150 or 330 mg) administered to 38 patients (aged 18–50).<sup>24</sup> Patients on testosterone reported significantly less of an increase in depressed mood over treatment than those on placebo. In addition, significant improve-

ments in depressed mood were seen in patients receiving testosterone who were depressed at baseline (54% of participants), whereas there was no change in those receiving placebo. Dropout was 13% overall.

Hill et al. administered growth hormone (15 mg/kg per day) to 14 female and 1 male patient receiving inpatient care for AN.<sup>19</sup> This medication was associated with fewer days to display normal orthostatic heart rate response to a standing challenge among the treatment group than among placebo group. No patient left this study.

Another group compared estrogen/progesterone (0.625 mg Premarin<sup>®</sup> or 5 mg Provera<sup>®</sup> per day) with nonmedication control in 48 women (aged 16–43).<sup>23</sup> The groups did not differ on bone density measures at 6 months. Dropout was 14% in the hormone group and 4% in the nonmedication group.

**TABLE 4. Results from behavioral intervention trials for AN in adults**

Source, Treatment, Sample Size, Quality Score	Study Location and Setting, Percent Female, Age	Significant Differences Between Groups
Pike et al., <sup>26</sup> CBT vs. nutritional counseling, enrolled: 33, dropouts: 9%, fair	US: outpatient; female: 100%; age range: 18–45	<b>At endpoint:</b> CBT associated with lower percentage of treatment failures, higher percentage of “good” outcomes, and longer time (weeks) to relapse, compared with nutrition counseling. <b>Change over time:</b> not reported
McIntosh et al., <sup>27</sup> CBT vs. IPT vs. NSCM, enrolled: 56, dropouts: 38%, fair	New Zealand: outpatient; female: 100%; age: 17–40	<b>At endpoint:</b> NSCM associated with higher likelihood of “good” global outcome than IPT <b>Change over time:</b> NSCM superior to IPT in improving global functioning and eating restraint over 20 weeks; NSCM superior to CBT in improving global functioning over 20 weeks; CBT superior to IPT in improving eating restraint over 20 weeks
Channon et al., <sup>28</sup> CBT vs. BT vs. “usual care” control, enrolled: 24, dropouts: 13%, fair	UK: outpatient; female: 100%; age, mean (SD)—CBT: 21.6 (5.9), BT: 24.1 (5.8), control: 25.8 (7.2)	<b>At endpoint:</b> <b>At 6-month follow-up:</b> CBT associated with better psychosexual functioning than BT. BT associated with greater improvement in menstrual functioning than CBT <b>At 12-month follow-up:</b> BT associated with better preferred weight than CBT. CBT and BT combined associated with greater improvements on nutritional functioning than control group. Control group showed greater improvements on drive for thinness than CBT and BT combined <b>Change over time:</b> not reported
Treasure et al., <sup>29</sup> CAT vs. EBT, enrolled: 30, dropouts: 33%, fair	UK: outpatient; female: 97%; age range: CAT, 18–35, EBT, 18–39	<b>At endpoint:</b> CAT associated with higher self-rating of improvement <b>Change over time:</b> not reported
Dare et al., <sup>30</sup> CAT vs. focal vs. family vs. “routine” therapy, enrolled: 84, dropouts: 36%, fair	UK: outpatient; females: 98%; age, mean (SD): 26.3 (6.7)	<b>At endpoint:</b> At 1-year follow-up, focal and family therapy associated with higher weight than routine treatment; higher percentage of patients in focal and family therapy were recovered or significantly improved (i.e., >85% IBW, no or few menstrual or BN symptoms) <b>Change over time:</b> not reported
Crisp et al. <sup>38</sup> and Gowers et al., <sup>34</sup> inpatient treatment vs. outpatient individual and family therapy and dietary counseling vs. group therapy and dietary counseling vs. no formal treatment, enrolled: 90, dropouts: 19%, fair	UK: inpatient and outpatient; females: 100%; age, mean (SD)—inpatient: 23.2 (4.9), outpatient individual: 21.2 (5.1), outpatient group: 19.7 (2.6), no formal treatment: 21.9 (4.5)	<b>At endpoint:</b> At 1-year and 2-year follow-up, outpatient family/diet counseling associated with higher weight and BMI compared with no formal treatment <b>Change over time:</b> <b>At 1-year follow-up:</b> weight increased more in all three active groups than in group with no formal treatment <b>At 2-year follow-up:</b> weight increased more in outpatient family/diet counseling than in group with no formal treatment

Notes: BN, bulimia nervosa; BT, behavioral therapy; CAT, cognitive analytic therapy; CBT, cognitive behavioral therapy; EBT, educational behavioral therapy; IPT, interpersonal therapy; NSCM, nonspecific supportive clinical management, SD, standard deviation; UK, United Kingdom; US, United States.

**Nutritional Supplements.** Birmingham et al. determined, in 54 women inpatients (older than 15 years), that 14 mg per day of zinc was associated with accelerated increase of BMI compared to placebo.<sup>25</sup> Dropout was high: 39% in zinc and 32% in placebo.

### Behavioral Interventions for AN

Behavioral intervention trials included all forms of psychotherapy (cognitive, supportive, dynamic, family, individual, and group). Specific therapeutic approaches included cognitive behavioral therapy (CBT),<sup>26–28</sup> cognitive analytic therapy (CAT),<sup>29</sup> focal

psychoanalytic therapy,<sup>30</sup> specialist supportive therapy,<sup>27</sup> therapeutic warming,<sup>12</sup> and various forms of family therapy.<sup>31–37</sup>

We rated two behavioral trials as good<sup>31,32</sup> and nine as fair.<sup>26–30,33,35,36,38</sup> Of these 11 trials, six focused solely on adults (~18 years and older) (Table 4); four focused on adolescents (mean ages 14–15 years), and one on both age groups (Table 5).

**Cognitive Behavioral Therapy.** CBT studies generally used a form of therapy tailored to AN that focused on cognitive and behavioral features associated with maintaining eating pathology. Of the three CBT studies, one followed inpatient weight resto-

**TABLE 5. Results from behavioral intervention trials for AN in adolescents only and adolescents and adults combined**

Source, Treatment, Sample Size, Quality Score	Study Location and Setting, Percent Female, Age	Significant Differences Between Groups
Eisler et al., <sup>31</sup> CFT vs. SFT, enrolled: 40, dropouts: 10%, good	UK: outpatient; female: 98%; age range: 12–18	<b>At endpoint:</b> not reported <b>Change over time:</b> CFT superior in reducing eating disorder-related traits, depression, and obsessiveness
Robin et al., <sup>35,37</sup> BFST vs. EOIT, enrolled: 24, dropouts: 8%, fair	US: outpatient and inpatient; female: 100%; age range: 12–19	<b>At endpoint:</b> none <b>Change over time:</b> BFST superior at posttreatment and 1-year follow-up in increasing BMI and superior in improving mother's positive communication at 1-year follow-up
Geist et al., <sup>33</sup> family therapy vs. family group psychoeducation, enrolled: 25, dropouts: 0%, fair	Canada: inpatient; female: 100%; age range: 12–17	<b>At endpoint:</b> none <b>Change over time:</b> none
Lock et al., <sup>32</sup> long-term vs. short-term family therapy, enrolled: 86, dropouts: 20%, good	US: outpatient; female: 90%; age range: 12–18	<b>At endpoint:</b> none <b>Change over time:</b> no differences on any measures among those with most severe YBC-EDS symptoms; Longer-term treatment associated with better BMI outcome in those with most severe eating disorder symptoms and with better EDE global outcome in those with nonintact families
Russell et al. <sup>36</sup> and Eisler et al., <sup>39</sup> family therapy vs. individual therapy, enrolled: 57, dropouts: 5%, fair	UK: outpatient; female: unknown; age range: 14–55	<b>At endpoint:</b> not reported <b>Change over time:</b> among early onset, less chronic patients, family therapy superior to individual therapy in improving nutritional status, menstrual and psychosexual function, and weight over 1-year treatment; family therapy more likely associated with a good outcome over 1-year treatment and 5-year follow-up

Notes: BFST, behavioral family systems therapy; BMI, body mass index; BT, behavioral therapy; CFT, conjoint family therapy; EDE, eating disorders examination; EOIT, ego-oriented individual therapy; SFT, separated family therapy; UK, United Kingdom; YBC-EDS, Yale-Brown-Cornell Eating Disorders Scale.

ration<sup>26</sup> and two were done in the underweight state.<sup>27,28</sup>

After inpatient weight restoration, Pike et al. showed that CBT significantly reduced relapse risk and increased the likelihood of good outcomes compared with nutritional counseling, based on nutritional education and food exchanges.<sup>26</sup> Of those receiving CBT, a greater number of individuals with good outcomes happened to be receiving antidepressant medication outside of the protocol which was allowed by the study design.

McIntosh et al. studied underweight AN outpatients and compared CBT with interpersonal psychotherapy (IPT) and nonspecific supportive clinical management (NSCM).<sup>27</sup> IPT for AN derives from IPT used for depression<sup>40</sup> and BN,<sup>41</sup> and focuses on one interpersonal problem area: interpersonal disputes, role transitions, grief, or interpersonal deficits. For this study, NSCM reflected the type of treatment an individual could receive in the community from a provider familiar with the treatment of eating disorders and incorporated elements of sound clinical management and supportive psychotherapy. In an intention-to-treat analysis, NSCM performed significantly

better than IPT in producing global good outcome ratings; CBT outcomes fell in between and were not significantly different from outcomes in the other two treatments.<sup>27</sup> Channon et al. compared CBT with behavioral therapy (BT) and a control group for 6 months.<sup>28</sup> At 12-month followup, CBT and BT combined improved nutritional functioning more than the control; however, the control group showed greater improvements in drive for thinness than the CBT and BT groups combined.

**Cognitive Analytic Therapy.** The two studies that utilized CAT, a treatment integrating psychodynamic and behavioral approaches, failed to find any advantage of CAT over educational BT or focal family therapy in eating, mood, or weight outcomes.<sup>29,30</sup> Focal family therapy focused on eliminating the eating disorder from its controlling role in determining the relationship between the patient and other family members.

**Family Therapy.** Two studies incorporated various forms of family therapy with adults<sup>30,34,38</sup>; four family therapy studies focused exclusively on adolescents<sup>31,33,35,37</sup>; and one combined adolescent and adult patients.<sup>36,39</sup>

Of the studies focusing on adults, Dare et al.<sup>30</sup> found focal family therapy to be superior to routine treatment, but equivalent to a CAT in increasing percentage of adult body weight, restoring menstruation, and decreasing bulimic symptoms; overall, clinical improvement was modest. Crisp et al. found outpatient individual and family therapy with variable numbers of sessions to be superior to referral to a family physician for increased weight at 1- and 2-year follow-up.<sup>34,38</sup>

In terms of family therapy with adolescents, Eisler et al. delivered a form of family therapy, focusing initially on parental control of re-nutrition in two different manners.<sup>31</sup> Conjoint therapy (family treated as a unit) provided a significant advantage over separated family therapy (parents and patient seen separately) on eating and mood outcomes but not on weight outcomes. Behavioral family systems therapy (BFST) is a form of family therapy in which parents take initial control of re-nutrition. Robin et al.<sup>35,37</sup> showed that, when combined with a common medical and dietary regimen, BFST was superior to ego-oriented individual therapy in increasing BMI and restoring menstruation, although neither therapy was superior on eating or mood outcomes. Another study found no differences between family therapy and family psychoeducation on any outcomes at 16 weeks.<sup>33</sup>

Addressing the issue of optimal duration of family therapy, Lock et al. randomized adolescents to either short (10 sessions over 6 months) or long (20 sessions over 12 months) family therapy, employing a manual-based model of initial parental control of refeeding model<sup>42</sup>; they found no differences on eating, psychiatric, or biomarker outcomes.<sup>32</sup> Longer-term family therapy suggested that those with more severe eating-related obsessions and nonin-tact families did better with longer treatment.

Finally, in the one study that included both adolescents and adults, Russell et al.<sup>36</sup> and later Eisler et al.<sup>39</sup> determined that family therapy was more effective for younger patients with earlier onset than for older patients with a more chronic course. Although few differences were observed across interventions, specific forms of family interventions did consistently show improvement over time with adolescent patients.

### **Harms of Treatments for AN**

The most common harm reported was the need for inpatient treatment among participants in an outpatient trial. In these cases, the events observed may be more ongoing features of the course of illness than an adverse event caused by the interven-

tion. Studies of behavioral interventions rarely report harms.

For the trials using second-generation antidepressants, we refer to recent publications on the comparative effectiveness and tolerability of second-generation antidepressants.<sup>43</sup> Common side effects associated with the use of second-generation antidepressants in major depressive disorder are nausea, headache, diarrhea, constipation, dizziness, fatigue, sweating, and sexual side effects. Rare but severe adverse events include hyponatremia, suicidality, and seizures. Up to 90% of patients experienced at least one adverse event during treatment. Overall, discontinuation rates attributed to adverse events did not differ significantly among individual drugs and ranged from 6 to 14%.

Given the small sample sizes and low completion rates of the two fluoxetine trials, we cannot determine whether harms associated with fluoxetine treatment in the underweight state differ in any way from treatment of normal-weight individuals with other psychiatric diagnoses. For tricyclic antidepressants, Halmi et al. reported sporadic cases of drowsiness, excitement, confusion, increased motor activity, tachycardia, dry mouth, and constipation associated with amitriptyline<sup>21</sup>; however, the rate of adverse events did not differ from placebo.

### **Factors Associated with Treatment Efficacy**

We found no consistent factors associated with better or poorer treatment outcome across studies. Indeed, subgroup analyses had very small samples, and conclusions must be viewed with extreme caution.

### **Treatment Efficacy by Subgroups**

No drug studies reported differential outcome by age. Only two drug trials<sup>19,22</sup> focused on the treatment of adolescent AN. Not a single drug study reported race or ethnicity of participants. No information exists regarding differential efficacy of pharmacotherapy interventions for AN by sex, gender, age, race, ethnicity, or cultural group.

In the psychotherapy trials, only two studies reported race and ethnicity of participants (in all: 10 Hispanic Americans, eight Asian Americans, no African Americans, and three individuals of "other" race or ethnicity). In no instance were results analyzed specifically by race or ethnic group. No data exist regarding differential efficacy of psychotherapeutic treatment for AN by sex, gender, race, ethnicity, or cultural group.

In terms of age, scant evidence shows that interventions involving the family have greater efficacy for individuals below the age of 15 than for patients

**TABLE 6. Strength of evidence for key questions for AN treatment**

Interventions and Age Groups	Treatment Outcomes	Harms of Treatment	Factors Associated with Efficacy	Differences by Sociodemographic Factors
	<b>Medications alone or medications and behavioral interventions</b>			
Adults	Weak	Weak	Weak	Nonexistent
Adolescents	Weak	Weak	Weak	Nonexistent
	<b>Behavioral interventions alone</b>			
Adults	Weak	Nonexistent	Weak	Nonexistent
Adolescents	Moderate	Nonexistent	Weak	Nonexistent

above that age. This information is based solely on studies by just one team of investigators who found family therapy to be more effective for adolescent AN patients with a shorter duration of illness than for adults with a more chronic course.<sup>36,39</sup> However, no definitive replications have been done. Moreover, no studies have explored the role of family therapy in adults focusing on the family of insertion rather than family of origin, which may be the relevant comparison, or other adaptation of family therapy for adults or adolescents.

## Conclusion

### *Strength of Evidence Base*

For our key questions, we found the strength of the evidence to be variable but generally unimpressive; no body of evidence on any issue was rated strong (Table 6). For treatment efficacy, we judged evidence to be weak; the exception was for psychotherapy for adolescents, which we rated moderately strong. The evidence for harms was weak with respect to pharmacotherapies and nonexistent for behavioral interventions. For factors associated with or influencing therapeutic outcome, we rated the literature as weak. Finally, for KQ4, differences in treatment outcome by age, sex, gender, race, ethnicity, or cultural group, we rated the literature as nonexistent (IV). The treatment literature for AN has virtually ignored all these factors.

### *Summary of the Evidence*

Managing individuals with AN with medication only is inappropriate, based on evidence reviewed here. No pharmacological intervention for AN has a significant impact on weight gain or the psychological features of AN. Although mood may improve with tricyclic antidepressants, this outcome is not associated with improved weight gain. Moreover, medication treatment for AN is associated with high dropout rates, suggesting that the currently available medications are not acceptable to individuals with AN.

For adult AN, we have tentative evidence that CBT reduces relapse risk for adults, after weight restoration has been accomplished. By contrast, we do not know whether the CBT approach is more helpful than others in the acutely underweight state, as one study found that a manual-based form of NSCM was more effective than CBT and IPT in terms of global outcomes during the acute phase. No replications of these studies exist.

Family therapy as currently practiced has no supportive evidence for adults with AN and a comparatively long duration of illness. Overall, family therapy focusing on parental control of renutrition is efficacious in treating younger nonchronic patients with AN; these approaches lead to clinically meaningful weight gain and psychological improvement. Although most studies of family therapy compared one variant of family therapy with another, two studies produced results suggesting that family therapy was superior to individual therapy for adolescent patients with shorter duration of illness.

Although many of the medication trials for AN were conducted within the context of basic clinical management, no study that systematically studied medication plus psychotherapy for AN met our inclusion criteria.

### *Shortcomings of the Literature*

Several serious deficiencies in the literature exist. Sample size was often insufficient to draw conclusions regarding differential efficacy across groups. Even when investigators did power calculations, they rarely made adequate allowance for attrition. Consequently, designs that contrasted one active approach with another (usually behavioral interventions) most commonly observed no differences across interventions. Even with small samples, many authors conducted subgroup analyses on outcome variables, often in the absence of *a priori* hypotheses, which can yield findings that arise by chance.

Attrition from clinical trials is especially problematic in AN studies.<sup>44</sup> AN is marked by denial, fear of weight gain (which is the key treatment out-

come), and hesitance to take medication. High attrition compromises the integrity of outcome data; differential attrition between treatment intervention groups and comparison (e.g., usual-care or placebo) groups is even more damaging. In light of high attrition, investigators often reported only completer analyses, a practice that potentially biases results. Substantial attention needs to be paid to enhancing motivation for treatment in individuals with AN and to improving retention in clinical trials.

Additional weaknesses of the AN treatment literature include insufficient rigor with respect to statistical design and analysis in both the planning and conduct of trials, poor or unclear randomization procedures, inadequate allocation concealment, inappropriate statistics for repeated measures designs, inattention to the effects of differential treatment duration, and excessive diagnostic and outcome assessment measures. Insufficient attention has been paid to addressing the optimal approach to treatment of serious long-term physical sequelae of AN, most notably osteoporosis.

No consensus definitions exist for stage of illness, remission, recovery, and relapse for this condition. Developing standardized definitions of these terms for AN and the means to evaluate them are high priorities for future research. In addition, greater attention to distinguishing between statistically significant and clinically meaningful differences is required.

The literature on AN has failed to distinguish sufficiently between interventions targeted at individuals before or after weight restoration and has failed to address the optimal approach to renutrition.

Indeed, whether medication and behavioral interventions have different outcomes depending on weight status remains murky. Given that low weight and malnutrition can interfere with the efficacy of medication and the ability to process information in psychotherapy, the optimal timing of the administration of drugs and therapy vis-a-vis weight restoration is a critical question that remains unaddressed.

The AN literature is devoid of medication studies for adolescents; drug trials have focused almost exclusively on adults. Future medication trials should explore medication efficacy in adolescents and the differential efficacy of medications between adolescents and adults.

Although males suffer from eating disorders, they are underrepresented in clinical trials of AN. When included, their numbers are usually too small to be analyzed separately or compared to females.

The majority of the literature on AN fails even to report the race and ethnicity of participants. All descriptions of participants should include this critical parameter. No studies of medication or behavioral interventions have addressed the issue of whether treatment efficacy differs by race or ethnic background.

To remedy this shortcoming, we must collect adequate epidemiologic data to provide critically needed information about the frequency with which eating disorders occur across racial and ethnic groups. Such data would provide guidance for planning targeted recruitment in clinical trials and enable researchers to set priorities for approaches to incorporating race and ethnicity into both treatment and outcome studies. In addition, further exploration of sociocultural factors (e.g., stigma) may also assist with understanding both underdetection and underrepresentation of racial and ethnic minorities in research studies.

The majority of AN treatment studies are small, single-site trials. The average sample size of 23 illustrates this point robustly. Future multisite trials will facilitate patient recruitment, enhance statistical power, enable meaningful subgroup analyses, buffer against high drop-out rates, and improve generalizability of results. Working in partnership with insurance companies to enable such trials in the current reimbursement milieu may be critical to success.

Clinical trials for AN, in particular, do not adequately reflect the type of treatment typically delivered in the community. Neither do they address some key challenges facing clinicians who treat this disorder in inpatient and partial hospitalization or residential settings.

For low-weight patients with AN, the first treatment challenge is weight restoration. Guidelines from the American Psychiatric Association suggest that individuals at 75% of IBW or lower are candidates for inpatient weight restoration, although many other factors influence level of care decisions. When facilities are available, weight restoration occurs in hospital, followed by various levels of step-down marked by increasing autonomy and exposure to real-life eating and emotional situations.

No clinical trials for AN address the optimal approach to inpatient weight restoration that can achieve the most lasting gain. This also includes nutritional trials of optimal approaches to renutrition. No studies address the appropriateness of the recommendation for hospitalization at 75% IBW. No studies address the optimal conditions under which a patient should be discharged from inpa-

tient treatment and stepped down to less-structured environments. Given the financial expense of prolonged inpatient hospitalizations and the toll on both patient and family, the conditions under which extended hospitalizations are superior to intensive outpatient management should be the focus of future studies.

Trials of medication or behavioral interventions for patients with AN do not routinely describe the degree of medical compromise or strategies to monitor for potential harm in malnourished patients. Indeed, behavioral intervention trials often completely overlook the fact that their interventions may have adverse effects on patients. Especially, given the high drop-out rates from AN trials, behavioral interventions should pay greater attention to both physical and psychological harms associated with interventions. All studies should report adverse events associated with interventions with these disorders. In addition, with AN, researchers should determine, especially within medication trials, whether adverse events differ between the underweight and the weight-restored state.

## Future Research Needs

Discovering new medications that target the core biological and psychological features of AN, address adverse medical sequelae such as osteoporosis, and enhance motivation and retention in medication trials are critically needed steps. Additional attention to drug augmentation strategies and combined psychotherapeutic and medication trials is recommended. Research on innovative medications and behavioral treatments is warranted, especially given the state of treatment of AN. Of special importance will be trials of novel medications that target core biological and cognitive features of the disorders and that are also acceptable to patients.

We should actively seek to adapt further various psychotherapeutic interventions that are tailored to the unique core pathology of AN, and that are both efficacious and acceptable to the patients. New behavioral interventions that target motivation to change and encourage retention in treatment are required. Further dismantling of complex therapies such as CBT to determine the active therapeutic components is also warranted.

Other fields are benefiting from the application of new information technologies to the treatment of illness. Adequately powered clinical trials that

include the use of email, the Internet, personal digital assistants, text messaging, and other technological advances to enhance treatment will add to future treatment development. These approaches may be well-suited to disorders marked by shame, denial, and interpersonal deficits and where availability of specialty care is limited.

Given the frequency with which multidisciplinary therapeutic approaches are tried, studies that directly address their benefits and optimal approaches to applying them are required.

Future AN studies require large numbers of participants, multiple sites, clear delineation of the age, race, and ethnicity of participants, and interventions that are tailored to the unique core pathology and medical sequelae of the illness.

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## References

1. Agras W, Brandt H, Bulik C, Dolan-Sewell D, Fairburn C, Halmi K, et al. Report of the National Institutes of Health Workshop on overcoming barriers to treatment research in anorexia nervosa. *Int J Eat Disord* 2004;35:509–521.
2. Berkman N, Bulik C, Brownley K, Lohr K, Sedway J, Rooks A, et al. Management of eating disorders. Evidence Report/Technology Assessment No. 135 (Prepared by RTI International—University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016). AHRQ Publication No. 06-E010. Rockville, MD: Agency for Healthcare Research and Quality, 2006.
3. West S, King V, Carey T, Lohr K, McKoy N, Sutton S, et al. Systems to rate the strength of scientific evidence. Evidence report, Technology Assessment No. 47. Rockville, MD: Agency for Healthcare Research and Quality, 2002.
4. Greer N, Mosser G, Logan G, Halaas G. A practical approach to evidence grading. *Jt Comm J Qual Improv* 2000;26:700–712.
5. Vandereycken W. Neuroleptics in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled study with sulphiride. *Br J Psychiatry* 1984;144:288–292.
6. Barbarich NC, McConaha CW, Halmi KA, Gendall K, Sunday SR, Gaskill J, et al. Use of nutritional supplements to increase the efficacy of fluoxetine in the treatment of anorexia nervosa. *Int J Eat Disord* 2004;35:10–15.
7. Ruggiero GM, Laini V, Mauri MC, Ferrari VM, Clemente A, Lugo F, et al. A single blind comparison of amisulpride, fluoxetine and clomipramine in the treatment of restricting anorexics. *Prog Neuropsychopharmacol Biol Psychiatry* 2001;25:1049–1059.
8. Brambilla F, Draisci A, Peirone A, Brunetta M. Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders. II. Anorexia nervosa—Binge-eating/purging type. *Neuropsychobiology* 1995;32:64–67.
9. Fassino S, Leombruni P, Daga G, Brustolin A, Migliaretti G, Cavallo F, et al. Efficacy of citalopram in anorexia nervosa: A pilot study. *Eur Neuropsychopharmacol* 2002;12:453–459.

10. Szmukler GI, Young GP, Miller G, Lichtenstein M, Binns DS. A controlled trial of cisapride in anorexia nervosa. *Int J Eat Disord* 1995;17:347–357.
11. Ricca V, Mannucci E, Paionni A, Di Bernardo M, Cellini M, Cabras PL, et al. Venlafaxine versus fluoxetine in the treatment of atypical anorectic outpatients: A preliminary study. *Eat Weight Disord* 1999;4:10–14.
12. Birmingham CL, Gutierrez E, Jonat L, Beumont P. Randomized controlled trial of warming in anorexia nervosa. *Int J Eat Disord* 2004;35:234–238.
13. Hall A, Crisp A. Brief psychotherapy in the treatment of anorexia nervosa. Outcome at one year. *Br J Psychiatry* 1987;151:185–191.
14. Pillay M, Crisp A. The impact of social skills training within an established in-patient treatment programme for anorexia nervosa. *Br J Psychiatry* 1981;139:533–539.
15. Thien V, Thomas A, Markin D, Birmingham CL. Pilot study of a graded exercise program for the treatment of anorexia nervosa. *Int J Eat Disord* 2000;28:101–106.
16. le Grange D, Eisler I, Dare C, Russell G. Evaluation of family treatments in adolescent anorexia nervosa: A pilot study. *Int J Eat Disord* 1992;12:347–357.
17. Robin AL, Siegel PT, Moyer AW, Gilroy M, Dennis AB, Sikand A. A controlled comparison of family versus individual therapy for adolescents with anorexia nervosa. *J Am Acad Child Adolesc Psychiatry* 1999;38:1482–1489.
18. Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? *Am J Psychiatry* 1998;155:548–551.
19. Hill K, Bucuvalas J, McClain C, Kryscio R, Martini RT, Alfaro MP, et al. Pilot study of growth hormone administration during the refeeding of malnourished anorexia nervosa patients. *J Child Adolesc Psychopharmacol* 2000;10:3–8.
20. Kaye W, Nagata T, Weltzin T, Hsu L, Sokol M, McConaha C, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001;49:644–652.
21. Halmi KA, Eckert E, LaDu TJ, Cohen J. Anorexia nervosa: Treatment efficacy of cyproheptadine and amitriptyline. *Arch Gen Psychiatry* 1986;43:177–181.
22. Biederman J, Herzog D, Rivinus T, Harper G, Ferber R, Rosenbaum J, et al. Amitriptyline in the treatment of anorexia nervosa: A double-blind, placebo-controlled study. *J Clin Psychopharmacol* 1985;5:10–16.
23. Klibanski A, Biller BM, Schoenfeld DA, Herzog DB, Saxe VC. The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. *J Clin Endocrinol Metab* 1995;80:898–904.
24. Miller KK, Grieco KA, Klibanski A. Testosterone administration in women with anorexia nervosa. *J Clin Endocrinol Metab* 2005;90:1428–1433.
25. Birmingham C, Goldner E, Bakan R. Controlled trial of zinc supplementation in anorexia nervosa. *Int J Eat Disord* 1994;15:251–255.
26. 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.
27. McIntosh V, Jordan B, Carter F, Luty S, McKenzie J, Bulik C, et al. Three psychotherapies for anorexia nervosa: A randomized controlled trial. *Am J Psychiatry* 2005;162:741–747.
28. Channon S, De Silva P, Hemsley D, Perkins R. A controlled trial of cognitive-behavioural and behavioural treatment of anorexia nervosa. *Behav Res Ther* 1989;27:529–535.
29. Treasure J, Todd G, Brolly M, Tiller J, Nehmed A, Denman F. A pilot study of a randomised trial of cognitive analytical therapy vs educational behavioral therapy for adult anorexia nervosa. *Behav Res Ther* 1995;33:363–367.
30. Dare C, Eisler I, Russell G, Treasure J, Dodge L. Psychological therapies for adults with anorexia nervosa: Randomised controlled trial of out-patient treatments. *Br J Psychiatry* 2001;178:216–221.
31. Eisler I, Dare C, Hodes M, Russell G, Dodge E, LeGrange D. Family therapy for adolescent anorexia nervosa: The results of a controlled comparison of two family interventions. *J Child Psychol Psychiatry* 2000;41:727–736.
32. Lock J, Agras WS, Bryson S, Kraemer HC. A comparison of short- and long-term family therapy for adolescent anorexia nervosa. *J Am Acad Child Adolesc Psychiatry* 2005;44:632–639.
33. Geist R, Heinmaa M, Stephens D, Davis R, Katzman D. Comparison of family therapy and family group psychoeducation in adolescents with anorexia nervosa. *Can J Psychiatry* 2000;45:173–178.
34. Gowers S, Norton K, Halek C, Crisp A. Outcome of outpatient psychotherapy in a random allocation treatment study of anorexia nervosa. *Int J Eat Disord* 1994;15:165–177.
35. Robin A, Siegel P, Koepke T, Moyer A, Tice S. Family therapy versus individual therapy for adolescent females with anorexia nervosa. *J Dev Behav Pediatr* 1994;15:111–116.
36. Russell GFM, Szmukler GI, Dare C, Eisler I. An evaluation of family therapy in anorexia and bulimia nervosa. *Arch Gen Psychiatry* 1987;44:1047–1056.
37. Robin AL, Siegel PT, Moyer A. Family versus individual therapy for anorexia: Impact on family conflict. *Int J Eat Disord* 1995;17:313–322.
38. Crisp A, Norton K, Gowers S, Halek C, Bowyer C, Yeldham D, et al. A controlled study of the effect of therapies aimed at adolescent and family psychopathology in anorexia nervosa. *Br J Psychiatry* 1991;159:325–333.
39. Eisler I, Dare C, Russell G, Szmukler G, leGrange D, Dodge E. Family and individual therapy in anorexia nervosa. A 5-year follow-up. *Arch Gen Psychiatry* 1997;54:1025–1030.
40. Klerman G, Weissman M, Rounsaville B, Chevron E. *Interpersonal Psychotherapy of Depression*. New York, NY: Basic Books, 1984.
41. Fairburn CG. Interpersonal psychotherapy for bulimia nervosa. In: Klerman G, Weissman M, editors. *New Applications of Interpersonal Psychotherapy*. Washington, DC: American Psychiatric Press, 1993, pp.355–378.
42. Lock J, Le Grange D, Agras W, Dare C. *Treatment Manual for Anorexia Nervosa: A Family-Based Approach*. New York: Guilford Press, 2001.
43. Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. *Ann Intern Med* 2005;143:415–426.
44. Halmi KA, Agras WS, Crow S, Mitchell J, Wilson GT, Bryson SW, et al. Predictors of treatment acceptance and completion in anorexia nervosa: Implications for future study designs. *Arch Gen Psychiatry* 2005;62:776–781.