

CLINICAL PRACTICE

Anorexia Nervosa

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 17-year-old girl is taken to her physician by worried parents. Never overweight, in the past six months she became determined to reduce from her baseline weight of 59.1 kg (130 lb). Her height is 1.7 m (5 ft 6 in.); her body-mass index (the weight in kilograms divided by the square of the height in meters) is 21. Through dieting and exercise, she lost 13.6 kg (30 lb) and stopped menstruating four months ago; her current body-mass index is 16. She denies having any problems and is annoyed that her parents, friends, and teachers are concerned. How should she be evaluated and treated?

THE CLINICAL PROBLEM

Anorexia nervosa is an eating disorder that usually begins in adolescence and is characterized by determined dieting, often accompanied by compulsive exercise, and, in a subgroup of patients, purging behavior with or without binge eating, resulting in sustained low weight. Other features include disturbed body image, heightened desire to lose more weight, and pervasive fear of fatness. The lifetime risk for the full disorder among women is estimated to be 0.3 to 1 percent (with a greater frequency of subclinical anorexia nervosa) and among men about a 10th of that rate.¹

The causes appear to be multifactorial, with determinants including genetic influences²; personality traits of perfectionism and compulsiveness^{3,4}; anxiety disorders³⁻⁵; family history of depression and obesity; and peer, familial, and cultural pressures with respect to appearance.⁶ These contribute to an entrenched overvaluation of slimness, distorted perceptions of body weight, and phobic avoidance of many foods. The diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition⁷ (DSM-IV), are shown in Table 1. Most authorities are increasingly flexible with regard to the criteria requiring dieting to below 85 percent of normal body weight for age and height and a duration of amenorrhea of more than three months. Few differences are found in the demographic characteristics and clinical features between patients who have the full syndrome of anorexia nervosa and those meeting all criteria except amenorrhea in female patients or decreased testosterone levels and diminished sex drive and function in male patients.⁸ Anorexia nervosa occurs in two types: food restricting, and binge eating and purging. The restricting type is characterized by marked caloric reduction, typically to 300 to 700 kcal per day, often accompanied by compulsive exercise. In the binge type, the binge may consist of food in a range from small amounts ("subjective" binge) to several thousands of calories. Purging usually begins after dieting commences, most commonly with the use of self-induced vomiting, or by abuse of laxatives, and occasionally with the use of diet pills or diuretic agents.

Other psychiatric conditions often coexist with anorexia nervosa, including major depression or dysthymia (in 50 to 75 percent of patients⁹), anxiety disorders (in more than 60 percent of patients¹⁰), and obsessive-compulsive disorder (in more than 40 percent of patients¹⁰). Alcohol or substance abuse may also be present (in 12 to 27 percent

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Table 1. Diagnostic Criteria for and Types of Anorexia Nervosa.***Diagnostic criteria**

Refusal to maintain body weight at or above a minimal normal weight for age and height (e.g., a weight loss resulting in maintenance of body weight at less than 85 percent of the expected weight or failure to make the expected weight gain during the period of growth, resulting in a body weight of less than 85 percent of the expected weight).

All the following are present:

An intense fear of gaining weight or becoming fat, even though underweight

A disturbance in the way in which body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of current low body weight

Among postmenarchal girls and women, amenorrhea (the absence of at least three consecutive menstrual cycles; amenorrhea is considered to be present if menstrual periods occur only after the administration of hormone [estrogen] therapy)

Type**Restricting type**

The patient has not regularly engaged in binge-eating or purging behavior (self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

Binge eating and purging type or purging type

The patient has regularly engaged in binge-eating, purging behavior, or both

* Estimates of healthy weight for a given patient are determined by the physician on the basis of historical considerations that often include the patient's growth charts and, for women, the weight at which healthy menstruation and ovulation resume, which may be higher than the weight below which menstruation and ovulation became impaired. Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.⁶

of patients^{9,11}) — more often among those with the binge–purging type of anorexia nervosa, among whom the rate of impulsive behavior is also higher, than among those with the restricting type.

Medical complications resulting from semistarvation, purging, or overexercising or a combination of these symptoms affect virtually every organ system. Common signs and symptoms include loss of subcutaneous fat tissue, orthostatic hypotension, bradycardia, impaired menstrual function, hair loss, and hypothermia. Many laboratory measures may be affected, among them serum electrolyte levels and thyroid function. Among patients who have anorexia nervosa in adolescence, medical complications may persist into the adult years.¹² Long-range concerns include osteopenia and osteoporosis; affected adolescents may have shorter stature than expected and high rates of stress fractures by their mid-20s.^{13,14} Abnormalities in cognitive function may also occur. The brain loses both white and gray matter during severe weight loss as a result of semistarvation; weight restoration results in the return of white matter to premorbid levels, but some loss of gray matter persists¹⁵ that may be associated with long-term effects on cognitive functioning. Women who have had anorexia nervosa also have higher rates of miscarriage and lower infant birth weights than do healthy women.¹⁶

Standardized mortality ratios (comparing mortality among persons with anorexia nervosa with that in the general population) are elevated¹⁷ for all

causes of death (ratio, 11.6), especially suicide (ratio, 56.9).¹⁸ Patients with the binge–purging type of the disorder and also alcohol and substance abuse have a higher risk of premature death than do other patients with anorexia nervosa.¹⁹ Death from medical causes results primarily from starvation or purging-related arrhythmias.²⁰ The probability of recovery appears to vary inversely with the severity of weight loss and the presence of coexisting psychiatric disorders, including highly avoidant or impulsive personality disorders.²¹

Full recovery of weight, growth and development, menstruation, normal eating behavior and attitudes with regard to food, and body shape and body weight occurs in 50 to 70 percent or more of treated adolescents. A prospective study of adolescents who received comprehensive treatment found that 76 percent no longer had a diagnosable eating disorder at 10 years of follow-up.²² Attaining complete physical and psychological health may take five to seven years.²³ Outcomes are poorer among adults with anorexia; only 25 to 50 percent of adults who require hospitalization recover.²⁴

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of anorexia nervosa is made on the basis of history taking (including information from family members, friends, and teachers) that reveals overvaluation of thinness and abnormal food re-

striction, compulsive exercise, and sometimes bingeing and purging and on the basis of a physical examination revealing excessive thinness. Purging is suggested by enlargement of the salivary glands (“chubby cheeks”), eroded dental enamel, and scars on the dorsum of the hands from repeated, self-induced vomiting. Meeting the criteria in Table 1 establishes the diagnosis; it is unnecessary to rule out all medical causes of weight loss.

No specific laboratory tests confirm the diagnosis. Table 2 summarizes the initial laboratory studies recommended to assess the physiological effect of anorexia nervosa. Dual-energy x-ray absorptiometry of bone is recommended, because osteopenia may occur within six months of the development of amenorrhea. Clinical experience suggests that documenting early osteopenia and making patients aware of the physiological effects of weight loss may help to motivate patients who do not readily acknowledge having the disease.

TREATMENT

At present, there have been few controlled trials to guide treatment,^{25,26} but numerous observational studies suggest that initial treatment should focus on prompt weight restoration.^{25,27,28} Because many patients enter treatment reluctantly, techniques that enhance motivation (involving encouragement to acknowledge the disease and to facilitate readiness to change)²⁹ are increasingly used to treat this condition, although no studies have yet confirmed their value. In the care of young children and adolescents, engaging the family is a necessary part of treatment.

Initial outpatient treatment often involves a primary care physician, a psychiatrist or psychologist familiar with anorexia nervosa, and a registered dietitian. Educating the patient and family is critical with regard to the nature of the illness, serious health risks, effective treatments, and the need for follow-up. Patients should be seen regularly, usually weekly, to monitor weight (as measured in the early morning, after voiding, in a hospital gown) and other physical and laboratory indicators, such as cardiovascular values and electrolyte levels, depending on the individual patient’s course. Care must be coordinated with other clinicians.

A caloric intake of approximately 1200 to 1500 kcal is usually recommended initially, with weekly increases of 500 kcal per day among outpatients for a weight restoration of 0.5 to 0.9 kg (1 to 2 lb) per week.²⁵ Indications for hospitalization, shown in Table 3, depend on the physiological and psychi-

atric status of the patient, the patient’s and the family’s motivation, the feasibility of outpatient weight restoration, and the availability of local resources. Adult patients whose weight is more than 25 percent below the expected weight (or with less weight loss if there are severe coexisting psychiatric or medical conditions, or both, or other pertinent considerations) and children or teenage patients who are losing weight rapidly, regardless of the percentage of body weight lost, generally require hospitalization to ensure food intake and to limit physical activity. Early intervention can reduce the risk of arrhythmia and the loss of cortical brain matter²⁵; it is also thought to prevent the disorder from becoming chronic, although data are lacking to support this view.

Observational data suggest that hospitalization in hospital units that specialize in the care of patients with eating disorders yields better outcomes than hospitalization in general medical units — a result that may be attributable to the nursing expertise and the use of effective protocols for refeeding (nutritional rehabilitation) and emotional care in the specialized units.³⁰ In severe cases, involuntary commitment to a psychiatric facility may be required. Short-term outcomes among patients who have been involuntarily committed are similar to those among patients admitted voluntarily.³¹

Refeeding

No particular nutritional regimen has proved to be superior, so long as adequate calories are supplied.³² Brisk improvement in nutritional status with few complications resulting from refeeding occurs when inpatients are started with 1200 to 1500 kcal per day and the intake is increased by 500 kcal every four days to about 3500 kcal (for female patients) to 4000 kcal (for male patients) per day. Supplemental overnight nasogastric feeding may slightly decrease the length of the hospital stay among children³³ but is not routinely recommended. Refeeding usually reduces apathy, lethargy, and food-related obsessions, although it does not generally eliminate them. Total parenteral alimentation is rarely appropriate.

Close monitoring is needed during starvation and refeeding, including monitoring of vital signs and attention to peripheral edema and cardiopulmonary function. A refeeding syndrome (reported in about 6 percent of hospitalized adolescents³⁴) may include minor abnormalities (e.g., transient pedal edema) or serious complications that require

Table 2. Recommended Laboratory Studies in Patients with Anorexia Nervosa.***Routine studies**

Complete blood count

Urinalysis

Measurement of serum electrolytes; levels of creatinine, thyrotropin, and phosphorus; and fasting glucose values†

Studies to consider for selected patients

Measurement of the level of serum amylase, for patients suspected of surreptitious vomiting‡

Measurement of serum calcium and magnesium levels and liver-function tests,§ for patients with weight below 75 percent of the expected weight; also, electrocardiogram (before initiation of atypical antipsychotic medications)

Dual-energy x-ray absorptiometry of bone, for patients who have been underweight for longer than six months

Magnetic resonance imaging or computed tomography of the brain and neuropsychological assessment for patients with atypical features, such as hallucinations, delusions, delirium, and persistent cognitive impairment, despite weight restoration

* Severely ill patients may have completely normal values on laboratory tests. Adapted from the *Practice Guideline for the Treatment of Patients with Eating Disorders* of the American Psychiatric Association, second edition.²⁵

† Patients in whom hypoglycemia is found on laboratory testing are frequently asymptomatic. Among those with the euthyroid sick syndrome, with decreased triiodothyronine (T3) and increased reverse T3 (its inactive isomer), this syndrome is common and often improves with weight restoration.

‡ Elevated serum amylase is primarily secreted by the salivary gland.

§ Hypocalcemia may result from chronic malnutrition or alkalosis and may be associated with changes on the electrocardiogram. A magnesium deficiency may result from malnutrition, diarrhea, or misuse of diuretic agents and may be associated with hypokalemia, hypophosphatemia, and changes on the electrocardiogram. Malnutrition may produce hepatomegaly, fatty liver, and rarely, cirrhosis. Elevated levels of liver enzymes may also reflect alcohol abuse or the use of medications with toxic effects on the liver.

urgent intervention (e.g., a prolonged QT interval or hypophosphatemia with associated weakness, confusion, and progressive neuromuscular dysfunction) (Table 2). This syndrome is most common among patients weighing less than 70 percent of their ideal body weight and in those receiving parenteral or enteral nutrition, although it can also occur in those receiving vigorous oral refeeding. Slower refeeding minimizes the risk of serious complications. Phosphorus, magnesium, and electrolyte levels and renal function should be followed closely, and supplements should be administered as needed. Clinical changes and laboratory values requiring immediate attention include altered consciousness, tachycardia, congestive heart failure, atypical abdominal pain, a prolonged QT interval or QT dispersion (a marker of abnormal ventricular repolarization associated with an increased risk of arrhythmia), serum potassium levels below 3 mmol per liter, and serum phosphorus levels below 0.8 mmol per liter (2.5 mg per deciliter).

The management of refeeding complications is guided by clinical experience, in the absence of studies. Peripheral edema is treated with leg elevation and withholding added salt from the diet; diuretics may exacerbate the edema, and their use should be avoided. Gastrointestinal symptoms are common during refeeding and often persist. Bloating, which

may be caused by slowed gastric emptying, may benefit from treatment with metoclopramide (at a dose of 5 to 10 mg one hour before meals and at bedtime). Gastroesophageal reflux usually improves with proton-pump-inhibitor therapy.

Short-term medical stabilization alone is inevitably insufficient. Because a brisk but medically safe weight gain among hospitalized patients averages 0.9 to 1.4 kg (2 to 3 lb) per week, inpatients who are 9.1 to 13.6 kg (20 to 30 lb) below their healthy weight may require two to three months of inpatient treatment. Rates of relapse and rehospitalization are higher among hospitalized patients who are discharged at low weights and before they and their families can assume responsibility for refeeding than among patients discharged at expected healthy weights, when they and their families can assume such responsibility.³⁵

To achieve full remission, ongoing care after discharge from the hospital is essential. It has been calculated that “adequate care” programs — modeled on usual care as delivered in the community — involving inpatient hospitalization lead to weight restoration (close to 100 percent of the ideal body weight). When followed by nearly three weeks of daytime hospital care, 50 sessions of psychotherapy, and 20 medication visits with fluoxetine treatment over two years, this program can prove to be more

cost-effective than usual care consisting of one week of hospitalization followed by less follow-up care over a shorter period.³⁶

Immediate Psychiatric Interventions

Controlled trials³⁷ and observational studies³⁸ have shown that selective serotonin-reuptake inhibitors (SSRIs) are ineffective in hastening weight gain in starved patients. Small open-label studies suggest that the use of atypical antipsychotic agents at low doses (e.g., olanzapine, at a dose of 2.5 to 10 mg per day) may improve weight gain, symptoms of depression, and obsessional thoughts, but controlled studies are lacking.³⁹⁻⁴¹

Data from controlled studies suggest that involving families of children and adolescents in the patients' care improves outcomes.^{42,43} For example, in one report, a subgroup of patients 18 years of age or younger who had been ill for three years or less and who were randomly assigned to receive family therapy had significantly better outcomes (with respect to weight gain, return of menses among female patients, and overall psychosocial functioning) at the fifth year of follow-up than similar patients who were assigned to individual psychotherapy,⁴³ although the numbers in the study were small. Outcomes of therapy were better among adolescent patients than among adult patients.

A Cochrane review²⁶ that included six small trials of psychotherapy in anorexia nervosa found that the data were insufficient to make the recommendation of any specific psychotherapy possible. However, it concluded that psychotherapy (including psychoanalytic therapy, cognitive behavioral therapy emphasizing the correction of distorted thoughts and self-defeating behavior, or cognitive analytic therapy involving features of both) resulted in improved restoration of weight, return of menses among female patients, and improved psychosocial functioning, as compared with routine treatment, which generally involves education and emotional support. Nevertheless, in the largest study, involving 84 adult patients, 62 percent of the patients had poor outcomes after a year of psychotherapy for anorexia nervosa.⁴⁴ In a recent controlled study involving acutely ill adult outpatients,⁴⁵ a structured course of psychotherapy involving advice, education, nutritional instruction, and support was as helpful as or superior to cognitive behavioral therapy or interpersonal psychotherapy (focused on conflicted relationships, losses, and role transitions such as changes in marital or employment status),

Table 3. Indications for Hospitalization.*

Suggested physiological values

Adults

- Heart rate <40 bpm
- Blood pressure <90/60 mm Hg
- Symptomatic hypoglycemia
- Potassium <3 mmol per liter
- Temperature <36.1°C (97.0°F)
- Dehydration
- Cardiovascular abnormalities other than bradycardia
- Weight <75 percent of the expected weight
- Any rapid weight loss of several kilograms within a week
- Lack of improvement or rapid worsening while in outpatient treatment

Children and adolescents

- Heart rate <50 bpm
- Orthostatic blood pressure resulting in increase in heart rate of >20 bpm or resulting in drop in blood pressure of >10 to 20 mm Hg
- Blood pressure <80/50 mm Hg
- Hypokalemia or hypophosphatemia
- Rapid weight loss even if the weight is not <75 percent below the normal weight
- Symptomatic hypoglycemia or fasting glucose <3.0 mmol per liter
- Lack of improvement or worsening despite outpatient treatment

Psychological indications

- Poor motivation or insight (inability to recognize the seriousness of severe weight loss), lack of cooperation with outpatient treatment
- Inability to eat independently or need for nasogastric feeding
- Suicidal plan, marked suicidal ideation
- Severe coexisting psychiatric disease
- Antitherapeutic family environment, especially if abuse present

* The term bpm denotes beats per minute. Adapted from the *Practice Guideline for the Treatment of Patients with Eating Disorders* of the American Psychiatric Association, second edition.²⁵

as assessed with the use of a global measure that incorporated weight and other criteria for anorexia nervosa and attitudes toward eating. However, weight gain itself did not differ among the patients according to type of psychotherapy, and overall, 70 percent of the patients had little improvement in weight or psychological measures.⁴⁵

Prevention of Relapse

After the patient demonstrates an ability to sustain initial improvements in regained weight and eating behavior, less intensive levels of ambulatory care may be resumed. One placebo-controlled trial involving patients who had regained weight showed that those taking fluoxetine at doses of 20 to 60 mg per day were more likely to maintain their weight gain and had fewer depressive symptoms after one year.⁴⁶ Among adults patients, cognitive behavioral therapy in particular may reduce the rate of relapse, as compared with nutritional counseling.⁴⁷ Family therapy is more effective than individual supportive therapy in preventing relapse among patients 18 years of age or younger.⁴⁴

Management of Bone Loss

In a randomized controlled trial, the use of combined estrogen–progestin oral contraceptives was found to be ineffective in improving bone density in patients with anorexia nervosa, as compared with standard treatment.⁴⁸ Supplementation with calcium and vitamin D is recommended, even though these supplements have not been shown to reverse skeletal deterioration in anorexia nervosa. Although the effects of such treatments as recombinant human insulin-like growth factor,⁴⁹ bone growth factors, and bisphosphonates⁵⁰ on bone loss are being studied, their role remains uncertain. Nutritional rehabilitation during the period of bone growth is effective in reversing bone loss.⁵¹

AREAS OF UNCERTAINTY

Randomized controlled trials are lacking for many interventions for patients with anorexia nervosa. High dropout rates and premature inpatient discharges are among the difficulties involved in studying this population. Research is needed to evaluate ways to match patients with specific treatments on the basis of clinical characteristics, to determine optimal methods of refeeding, to assess medications for weight restoration more effectively, to treat complications of excessive weight loss, and to determine which psychotherapeutic approach may be best for specific patient groups.

RECOMMENDATIONS FROM GUIDELINES

Available treatment guidelines include those from the American Psychiatric Association,²⁵ the National Institute for Clinical Excellence in Britain,⁵² the Australian and New Zealand Royal College of Psychiatry,²⁷ pediatric groups,^{53,54} and the American Dietetic Association.⁵⁵ All of them stress the paucity of controlled trials and the need for better research. These guidelines generally concur with the recommendations presented here.

SUMMARY AND CONCLUSIONS

In the case of a patient such as the adolescent described in the vignette, the history taking and physical examination should assess the patient's condition with regard to diagnostic features of anorexia nervosa, including history of weight loss, changes

in menses, nutritional patterns, binge–purging behavior, compulsive exercise, preoccupation with eating and weight, distorted body image, and any coexisting psychiatric conditions. Family and friends should be questioned, particularly in the case of younger patients, who may dismiss the concern that they may have anorexia nervosa or even deny that any weight loss has occurred.

Initially, this patient may be treated by her primary care physician who should be in close, regular contact with both a psychiatrist or psychologist knowledgeable about anorexia nervosa and a registered dietitian. The therapeutic approach should focus on educating the patient and her family about the disorder, its risks, and the benefits of treatment, including increasing caloric intake and reducing pathologic behaviors and attitudes. The refeeding plan may be instituted by the family working with the patient and in consultation with the dietitian. The caloric intake should be progressively increased over one or two weeks to a level at which a weight gain of 0.5 to 0.9 kg (1 to 2 lb) per week is achieved and expanded food choices are presented. The patient should be weighed in a consistent manner and on the same scale at least weekly.

If purging, edema, or cardiovascular signs or symptoms appear, close clinical and laboratory follow-up should be undertaken. Treatment should include frequent family meetings and psychotherapy aimed at fostering healthful eating and minimizing distress about food, body weight, and body shape; no individual therapy has been proved to be superior to other approaches, but education, advice, and support should be prominent features. The patient should remain in treatment for one to two years after weight restoration to prevent relapse. After weight restoration, ongoing psychotherapy that incorporates cognitive behavioral methods and the use of an SSRI such as fluoxetine, at 20 to 60 mg per day, may help to decrease her risk of relapse. If the patient continues to lose weight or fails to gain weight after two weeks, hospitalization is warranted, preferably in a specialized unit, after which a specific aftercare plan, such as the one described above, should be implemented.

ADDENDUM

Specialist practitioners may be found through the Academy for Eating Disorders (www.aedweb.org). The National Eating Disorders Association (www.ned.org).

nationaleatingdisorders.org) and the National Association of Anorexia Nervosa and Associated Disorders (www.anad.org) provide resources for patients and families.

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