

## CLINICAL PRACTICE

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## 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 16-year-old was brought to a pediatrician's office by her parents for evaluation. She was visiting the doctor reluctantly and said that she had no health concerns. However, her parents reported that for 5 months she had been eating a highly restrictive diet consisting mainly of vegetables and small amounts of chicken or turkey, had declined to increase her food intake, and was progressively losing weight. On examination, her body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 17.5 (weight, 108 lb [49 kg], and height, 5 ft 7 in. [170 cm]). Her blood pressure while sitting was 100/78 mm Hg, which decreased to 78/60 mm Hg after she stood for 3 minutes. Her resting pulse was 46 beats per minute. Her skin was dry, and her hair was thinning at her scalp. An examination of her oral cavity revealed extensive erosion of the dental enamel. How would you further evaluate and treat this patient?**

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## THE CLINICAL PROBLEM

**A**NOREXIA NERVOSA IS A SEVERE PSYCHIATRIC DISORDER THAT IS CHARACTERIZED by starvation and malnutrition, a high incidence of coexisting psychiatric conditions, treatment resistance, and a substantial risk of death from medical complications and suicide. The diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association, fifth edition,<sup>1</sup> are shown in Table 1. An absolute cutoff in terms of low BMI is not stipulated, since several other factors warrant consideration, including the patient's age, sex, BMI before the occurrence of symptoms, and rapidity of weight loss; however, a low body weight (e.g., BMI  $\leq 17.5$ ) is usually observed in adults with anorexia nervosa. BMI-for-age growth charts are used to assess BMI in youths. Intense fear of weight gain is a central feature; however, patients often deny this, and it must be inferred from their behavior. An extreme focus on body weight and shape is integral to the disorder, combined with complete control over everything that is eaten, including the preparation of food.<sup>2</sup>

The two designated subtypes of anorexia nervosa are the restricting subtype, which is characterized by dietary restriction, and the binge-eating and purging subtype, in which restriction is accompanied by binge eating, purging, or both<sup>1</sup>; the condition may progress from one subtype to another. The restricting subtype is associated with an earlier age of onset, a better prognosis, and a greater likelihood of crossover to the other subtype.<sup>3,4</sup> The onset of anorexia nervosa usually occurs in adolescence or young adulthood. In the United States, the lifetime prevalence of the condition is approximately 0.80%.<sup>5</sup> Approximately 92% of affected



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## KEY CLINICAL POINTS

**ANOREXIA NERVOSA**

- Anorexia nervosa is a severe psychiatric disorder characterized by starvation and malnutrition, a high prevalence of coexisting psychiatric conditions, marked treatment resistance or no response to treatment, frequent medical complications, and a substantial risk of death.
- Anorexia nervosa has two subtypes: binge eating, purging, or both, and food restricting only. Anorexia nervosa often progresses from one subtype to another, particularly from the restricting subtype to the bingeing–purging subtype.
- Indications for hospitalization include profound hypotension or dehydration, severe electrolyte abnormalities, arrhythmias or severe bradycardia, suicide risk, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 15 or less.
- Several psychotherapeutic approaches are used in management. For children and adolescents, family-based treatments are commonly used.
- Psychotropic medications are generally ineffective in promoting weight gain, reducing depressive symptoms, or preventing relapse in patients with anorexia nervosa.

persons are female.<sup>5</sup> It occurs less commonly among non-Hispanic black and Hispanic populations than among white populations,<sup>5</sup> and the global incidence is increasing, particularly in Asia and the Middle East.<sup>6,7</sup>

Coexisting psychiatric conditions include major depression, anxiety disorders, obsessive–compulsive disorder, trauma-related disorders, and substance misuse (which is less common in patients with the restricting subtype).<sup>8</sup> The suicide risk among patients with anorexia is high, with an estimated incidence that is 18 times as high as that in controls.<sup>9</sup> The long-term course is heterogeneous, with 20-year longitudinal studies suggesting full remission in approximately 30 to 60% of patients, chronic illness in 20%, and residual symptoms in the remainder.<sup>10,11</sup> The incidence of relapse after treatment ranges from 9 to 52%, with most studies showing an incidence of at least 25%.<sup>12,13</sup> Anorexia nervosa is associated with a high mortality, with an aggregate mortality nearing 5.6% per decade.<sup>14</sup> Outcome studies show persistence of coexisting psychopathology,<sup>15</sup> which correlates with the presence and severity of symptoms of an eating disorder.<sup>16</sup> Recovery is often gradual; a long-term follow-up study showed recovery in approximately 31% of patients at 9 years but in almost two thirds of patients by 22 years.<sup>12</sup>

A high incidence of familial aggregation has been reported, with twin-based heritability estimates of 50 to 60%.<sup>17</sup> Recently, a genomewide association study identified eight risk loci for anorexia nervosa that were also predictive of other psychiatric disorders as well as a low BMI and metabolic derangements.<sup>17</sup>

Other risk factors include a history of trauma and living in a society in which a high value is placed on thinness,<sup>18,19</sup> although anorexia nervosa develops in only a small percentage of such populations, which suggests that dieting behaviors may trigger anorexia nervosa among vulnerable persons.<sup>20</sup> Perinatal factors that have been associated with an increased risk include in utero exposure to rubella as well as multiple birth and preterm birth.<sup>20,21</sup> Psychological risk factors include perfectionism, cognitive rigidity (e.g., reliance on rules), and childhood anxiety disorders.<sup>22</sup>

Medical complications are related to weight loss, malnutrition, and conditions attributable to purging.<sup>23</sup> Patients who engage in self-induced vomiting may have salivary-gland hypertrophy and, at times, elevated levels of serum amylase. They may have delayed gastric emptying, postprandial fullness, and bloating. Rarely, binge eating can be associated with gastric dilatation that can result in rupture; rarely, vomiting may result in esophageal rupture. Intermittent constipation and, more rarely, diarrhea can occur. Cardiovascular abnormalities include bradycardia (which can be severe when the heart rate slows during sleep), hypotension (particularly orthostatic hypotension), arrhythmias, and prolongation of the QT interval. The glomerular filtration rate may decline over time, particularly among patients with the bingeing–purging subtype; chronic volume depletion and hypokalemia are commonly implicated. In one study, end-stage renal disease had developed in 5.2% of patients with anorexia at a 21-year follow-up.<sup>24</sup> The bone marrow becomes atrophic. The hemoglobin level

and white-cell count may be reduced (with a relative sparing of lymphocytes); rarely, the platelet count may be low. Loss of muscle mass occurs and can result in difficulty standing after sitting. Osteoporosis, predisposing to fracture, develops in approximately one of three patients.<sup>25,26</sup>

Brain imaging studies show abnormalities (e.g., sulcal widening, ventricular dilatation, and cerebral atrophy) that often resolve with restoration of weight, but they sometimes persist.<sup>27</sup> Similarly, neurocognitive patterns, including cognitive rigidity, may improve or persist with restoration of weight.<sup>28,29</sup>

## STRATEGIES AND EVIDENCE

The evaluation requires a detailed medical, psychiatric, and nutritional assessment, physical examination (including measurement of height and weight), and laboratory testing (Table 2). Information should be obtained from the patient's caregivers as well as from other medical providers to corroborate the patient's self-report. Misinformation from the patient may result from fear of forced treatment, lack of self-awareness, and cognitive effects of malnourishment. A collaborative approach appears to enhance the patient's trust. Clinically, motivational interviewing techniques have been reported to be helpful in patients who are ambivalent, fearful, or antagonistic.<sup>30,31</sup> Questions can be framed to avoid judgment (e.g., "I am curious about your limiting your eating to one meal a day. What is that like for you?"). Similarly, empathetic and validating acceptance of the patient's reluctance to engage in treatment appears to be useful (e.g., "Based on what you have described to me about your previous experiences, your skepticism is understandable").

## TREATMENT

### HOSPITALIZATION AND RESIDENTIAL AND DAY TREATMENT

Immediate hospitalization is indicated in some patients<sup>23,24</sup> because of profound hypotension and dehydration, severe electrolyte abnormalities, arrhythmias or severe bradycardia, and suicide risk. Generally, a BMI of 15 or less indicates that hospitalization is warranted.<sup>24</sup> Rarely, consideration must be given to seeking involuntary treatment when the patient presents with signs and

**Table 1. Diagnostic Criteria for and Subtypes and Severity of Anorexia Nervosa.**

#### Diagnostic criteria\*

Restriction of energy intake relative to requirements, leading to significantly low body weight for the patient's age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than the minimal normal weight or, in children and adolescents, less than the minimal expected weight.

Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though the patient has a significantly low weight.

Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

#### Subtype designation

Restricting type: During the past 3 months, the patient has not engaged in recurrent episodes of binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). Weight loss is accomplished primarily through dieting, fasting, excessive exercise, or all of these methods.

Binge-eating and purging type: During the past 3 months, the patient has engaged in recurrent episodes of binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

#### Current severity

Mildly severe low body weight is defined as a BMI of  $\geq 17$ .<sup>†</sup>

Moderately severe low body weight is defined as a BMI of 16–16.99.

Severe low body weight is defined as a BMI of 15–15.99.

Extremely severe low body weight is defined as a BMI of  $< 15$ .

\* These three criteria, all of which are required for a diagnosis of anorexia nervosa, are from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.

† A patient who has undergone bariatric surgery may be considered to have mildly severe low body weight even with a BMI of 22 if the patient continues to "feel fat," have symptoms of starvation, and persist in severely limiting energy intake in order to achieve further weight loss.

symptoms that are deemed to be life-threatening.<sup>32</sup> Refeeding protocols traditionally were initiated with 1200 kcal per day to minimize the risk of refeeding syndrome. However, recent data suggest that more aggressive refeeding protocols (with monitoring for refeeding syndrome) are safe for the majority of patients.<sup>33</sup>

For patients for whom immediate hospitalization is not warranted (or for those who have already been hospitalized), alternatives to outpatient treatment include residential treatment and day treatment. Decisions regarding the treatment setting are guided by the severity and chronicity of the illness, insurance coverage, and resources available in the community. Residential treatment has become more common, with the goal of preventing relapse and chronicity; however, available studies have not shown better

<b>Table 2. Recommended Evaluation in Patients with Suspected Anorexia Nervosa.</b>	
<b>Evaluation</b>	<b>Findings in Patients with Anorexia Nervosa*</b>
<b>Patient characteristics</b>	
BMI	Low BMI ( $\leq 16.5$ ) <sup>†</sup>
Weight history	Progressive weight loss or inadequate weight gain
Duration of weight problems	Highly variable duration
Menstrual status	Irregular menses, amenorrhea
Eating patterns, foods avoided, and rules about food	Reduced intake and avoidance of fats and calorie-dense foods
Binge eating and loss of control while eating	Binge eating, loss of control while eating in some patients
Purging behavior	Self-induced vomiting; misuse of laxatives, diuretics, or enemas
Exercise	Excessive; patient exercises despite injury and feels driven or compelled to exercise
Body checking	Frequent mirror checking and measuring of body parts
Weighing	Frequent, multiple times per day
Dissatisfaction with body	Severe, pervasive; patient “feels fat” (sometimes in the overall body, sometimes in specific body parts)
Fear of weight gain	Severe, pervasive
Preoccupation with weight and shape	Dominates thinking
Self-esteem	Strongly influenced by body weight and shape and control of overeating behavior
Current or past suicidal ideation or plans	May be present
Self-injurious behavior (e.g., cutting or burning)	May be present
Current or past depression, anxiety, obsessive–compulsive disorder, trauma, or post-traumatic stress disorder	Often present
Misuse of alcohol and drugs (including diet pills)	May be present
Current or past psychiatric treatment	May be present
Psychosocial history	Extensive history
<b>Physical examination</b>	
Blood pressure	Hypotension (particularly orthostatic)
Temperature	Low
Pulse	Bradycardia, arrhythmias
Skin	Dry skin, hair loss at scalp, lanugo
Mouth	Erosion of dental enamel, poor dentition <sup>‡</sup>
Salivary glands	Hypertrophy (particularly parotid) <sup>‡</sup>
Fluid status	Evidence of dehydration (e.g., dry skin, orthostatic hypotension, but usually not tachycardia)
Arms and legs	Muscle wasting, edema (may occur with hypoalbuminemia or with refeeding)
<b>Laboratory tests</b>	
Complete blood count and differential count	Typically mildly low, with relative lymphocytosis
Platelet count	May be reduced
Serum electrolyte levels	
Sodium	Decreased
Potassium	Decreased
Chloride	Decreased
Bicarbonate	Increased

Table 2. (Continued.)	
Evaluation	Findings in Patients with Anorexia Nervosa*
Endocrine tests	
Triiodothyronine (T <sub>3</sub> )	Decreased
Reverse T <sub>3</sub>	Increased
Metabolic tests	
Calcium	Normal
Phosphorus	Decreased
Magnesium	Decreased
Fasting blood glucose	Decreased
Albumin	Decreased
Prealbumin	Decreased
Cholesterol	Increased
Amylase‡	Increased
Dual-energy x-ray absorptiometry	Osteopenia, osteoporosis
Electrocardiography	Bradycardia, prolongation of the QT interval, arrhythmias

\* Most of the findings listed are not invariably present; their occurrence depends on associated behaviors and the severity and chronicity of the illness.

† A low BMI is not required for the diagnosis of anorexia nervosa. For example, anorexia nervosa may be diagnosed in a person who has excessive weight loss after bariatric surgery, when symptoms of starvation are present and further weight loss is desired, but the BMI is not in a low range.

‡ These findings are suggestive of purging.

outcomes with residential treatment than with day treatment or outpatient treatment.<sup>34</sup>

#### PSYCHOTHERAPY

Psychotherapy is the mainstay of therapy. However, data to guide choices among types of psychotherapy remain limited and controversial.

Family interventions, particularly family-based treatment, are commonly recommended in the treatment of children and adolescents.<sup>35</sup> Such interventions are typically delivered in three phases over a period of 6 to 12 months. The first phase emphasizes the role of the patient's parents in promoting healthy eating behaviors and weight restoration and helps families "unite" against the eating disorder rather than assigning blame. Caregivers typically have high levels of anxiety, stress, and depression, and they often feel helpless in confronting their child or teenager's restrictive eating and other problematic behaviors<sup>36</sup>; by providing structure and support, this approach may help reduce parental distress. Parents carefully monitor all of the patient's eating and activities to prevent excessive exercise and purging. As treatment progresses into the second phase, autonomy in feeding is gradually shifted back to the child or teenager. The third

phase focuses on facilitating improved family communication and independence. Clinical experience and randomized trials have suggested that this form of therapy is more beneficial than other treatments, with rates of remission (defined as weight restoration and improvement in cognitive function) at the end of treatment and up to 12-month follow-up ranging from 30 to 60%, with small-to-medium effect sizes; weight gain early in treatment has been shown to predict better outcomes.<sup>37,38</sup> However, a recent Cochrane database review that included 25 trials showed a substantial risk of bias in many of the studies and concluded that there is limited low-quality evidence to support family therapy approaches over "treatment as usual,"<sup>39</sup> although this conclusion has been criticized.<sup>40</sup>

Emerging data support multifamily treatment, a variant in which parents of children with eating disorders provide support to each other. One multicenter trial showed better outcomes at 1 year with multifamily therapy than with usual family therapy.<sup>41</sup>

Cognitive behavioral therapy (CBT) approaches, which target eating and exercise behaviors as well as negative thoughts about eating, weight, and body shape, have inconsistent support as an

outpatient therapy in adolescents and adults.<sup>42</sup> An enhanced version of CBT generally involves 40 sessions, as compared with approximately 20 sessions for usual CBT.

Other types of psychotherapy are also used in adults and older adolescents. Maudsley Anorexia Treatment for Adults uses individually targeted behavioral, educational, and motivational approaches to address perpetuating features of anorexia nervosa, including inflexible thinking and fear of making mistakes, interpersonal and emotional problems, beliefs about positive aspects of having anorexia nervosa, and the response of family members and significant others. Specialist-supportive clinical management involves provision of support, education, and encouragement to help the patient increase nutrient intake and regain weight, while allowing the patient to guide much of the therapy content. Focal psychodynamic therapy involves identification of foci for therapy, followed by three phases of treatment geared toward understanding how eating behaviors relate to the patient's beliefs, self-esteem, and relationships.

A randomized trial involving adults with anorexia nervosa compared outcomes of enhanced CBT,<sup>43</sup> the Maudsley Model of Anorexia Treatment for Adults, and specialist-supportive clinical management. At 1-year follow-up, the percentages of patients who had achieved a healthy body weight and remission (mean, 50% and 28%, respectively) did not differ significantly among the groups; however, 40% of the participants did not complete treatment. Another randomized trial involving adults that compared enhanced CBT with focal psychodynamic therapy and a form of usual treatment likewise showed no significant difference in the increase in BMI at the end of treatment or at 1 year among the treatment groups.<sup>44</sup> Similarly, a recent network meta-analysis including 18 randomized, controlled trials and 17 naturalistic studies of psychotherapies for adolescents and adults showed that available data, although limited, did not support the superiority of any one treatment over another.<sup>45</sup>

#### PHARMACOTHERAPY

Most psychopharmacologic agents are not effective in the treatment of anorexia nervosa.<sup>46</sup> Randomized trials have generally shown that various antidepressant drugs, when used in combination

with psychotherapy, are not more effective than psychotherapy alone in increasing weight, ameliorating depressive symptoms, or reducing the incidence of relapse among patients with anorexia nervosa.<sup>47</sup> Similarly, although some studies have suggested a modest benefit of second-generation antipsychotic drugs as a means of stimulating appetite and promoting weight gain, overall the results have been discouraging.<sup>46</sup> Despite the lack of efficacy of psychotropic drugs, they continue to be prescribed for patients with anorexia nervosa.<sup>48</sup>

#### MANAGEMENT OF BONE LOSS

Osteoporosis is a major concern in patients with anorexia nervosa.<sup>25,26</sup> Weight restoration (with a goal of resumption of menses) to improve bone density is the primary strategy for management. In addition, adequate calcium intake (generally 1200 to 1500 mg per day) is routinely recommended for all patients with anorexia nervosa, along with vitamin D supplementation when the blood level of this vitamin is low. Whereas oral contraceptives have not appeared to be effective for reducing bone loss in patients with anorexia nervosa (a finding attributed at least in part to the suppression of insulin-like growth factor 1 [IGF-1]),<sup>25,26</sup> some evidence supports the use of transdermal estrogen (which does not suppress IGF-1); a randomized trial involving 110 young patients with anorexia nervosa showed significantly higher spine and hip z scores over a period of 18 months with transdermal estrogen and cyclic progesterone than with placebo.<sup>27,49</sup> In adults with anorexia nervosa who have osteoporosis, limited data support a benefit of bisphosphonates, but additional studies are lacking, and these agents are generally not used in adolescents.<sup>27</sup>

#### AREAS OF UNCERTAINTY

Well-conducted randomized trials of psychotherapies which include long-term follow-up are needed. In addition, additional data from randomized trials of interventions to treat bone loss in this population are lacking.

Further study of approaches to prevent anorexia nervosa is also warranted. A systematic analysis of randomized trials suggested a benefit of some interventions. Among patients who were considered to be at increased risk, "dissonance-based interventions," which seek to intro-

duce more realistic attitudes about issues such as weight, appeared to be most effective at reducing risk. For patients with features of eating disorders but no established diagnosis, a CBT approach appeared to be effective.<sup>50</sup> However, the majority of trials had methodologic limitations,<sup>51</sup> and the cost-efficacy of such strategies is unclear.

#### GUIDELINES

Guidelines from the American Psychiatric Association for the management of anorexia nervosa were most recently updated in 2010<sup>52</sup>; those from the National Institute for Health and Clinical Excellence were updated in 2017,<sup>53</sup> and those from the American Academy of Child and Adolescent Psychiatry were updated in 2015.<sup>54</sup> Recently published updated guidelines from Germany are also available (2019).<sup>55</sup> The present treatment recommendations are generally consistent with these guidelines.

#### CONCLUSIONS AND RECOMMENDATIONS

The low BMI, marked weight loss, restricted eating behavior, and physical examination in the adolescent patient described in the vignette strongly suggest the diagnosis of anorexia nervosa, most likely the binge-eating and purging subtype given the extensive erosion of dental enamel. Although the patient initially did not report any problem, we would attempt to use motivational interviewing techniques to obtain information, and we would also obtain a history from her parents (Table 2). Testing should include measurement of levels of serum electrolytes, calcium, phosphorus, magnesium, fasting blood glucose, albumin, prealbumin, amylase, and lipids, a complete blood count and platelet count, and electrocardiography. Her low blood pressure and bradycardia are troubling; especially if she also has marked electrolyte derangements, we would be inclined to recommend at

least a brief hospitalization, on an eating disorders unit if available. During hospitalization, her care should involve both a child psychiatrist and pediatric specialists, further interview of the patient with discussion of anorexia nervosa as the problem, administration of intravenous fluids (and potassium and phosphorus replacement, as needed), and initiation of refeeding. Assuming the patient begins to more openly discuss her problems and behaviors and is not actively suicidal, we would recommend that once her condition is medically stable, she be discharged to begin family-based therapy with weekly sessions in the clinic. Although rigorous data are lacking to support any one type of psychotherapy over another, family-based approaches are preferred for children and adolescents.

The initial focus would be on working collaboratively with the patient to increase her food intake, stop purging behaviors, and regain weight, with her parents assuming a supervisory role, while she undergoes weekly medical and laboratory monitoring. The longer-term plan would be to increasingly emphasize her independence and establish effective family communication, with an expected reduction in the frequency of family-intervention sessions after 6 months. Although we would anticipate that she would continue to have some body-image disturbance and some anxiety about consuming high-fat and high-calorie foods, goals would include eating independently, attending school, participating in extracurricular activities, socializing with peers, and achieving a weight of at least 90% of a normal weight range for her height and age. She should continue to be monitored by her parents and periodically by a clinician for at least a year for any evidence of relapse, which would indicate the need to promptly reinstate therapy. Pharmacologic therapy is generally not indicated for the management of anorexia nervosa.

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Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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