Chapter e83: Eating Disorders

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KEY CONCEPTS

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1. Eating disorders are more commonly recognized than years past although patients are likely to not seek help and medication treatment options are limited.

2. Symptoms common to eating disorders include excessive intake of calorie-laden food over a short period of time (eg, binge eating or bingeing), and inappropriate compensatory behaviors to expend calories such as self-induced vomiting, the overuse of laxatives, diuretics, enemas, fasting, or excessive exercise (eg, purging behaviors).

3. Shifting between different eating disorder diagnostic categories is possible, especially if treatment does not result in symptom remission.

4. Psychiatric comorbidities are common with all forms of eating disorders. The differential diagnosis should generally include evaluation for depression, schizophrenia, generalized anxiety, obsessive-compulsive disorder (OCD), and personality disorders.

5. Calories must be gradually introduced during caloric restoration to prevent the potentially fatal complication known as refeeding syndrome. Failure to restore calories quickly enough may result in an unfeeding syndrome.

6. Clinicians must monitor closely for suicidality and educate individuals appropriately, similar to patients with major depressive disorder taking antidepressants, as mortality from suicide is not uncommon.

7. The treatment approach for anorexia nervosa (AN) includes a minimum of 6 months of psychotherapy, preferably cognitive behavioral therapy (CBT), in adults and family-based therapy in children. There are no FDA-approved agents for the treatment of AN.

8. Despite limited data, antidepressants in combination with nonpharmacologic treatment are the preferred pharmacotherapy for the acute and maintenance phases of bulimia nervosa (BN). Fluoxetine is the only FDA-approved medication to treat adult BN.

9. Use of selective serotonin reuptake inhibitors (SSRIs) and topiramate for the treatment of binge-eating disorder (BED) along with CBT and interpersonal psychotherapy (IPT) is supported by the literature. Lisdexamfetamine is the sole FDA-approved agent for BED.

10. It is important to transition patients being treated for AN gradually to outpatient care as there is a high risk of relapse within the first 60 days of inpatient refeeding.

BEYOND THE BOOK

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Watch the video entitled "After Anorexia: Life's too short to weigh your cornflakes" (*https://www.youtube.com/watch?v=gZpcTVqpaPw*), a TEDx Talk from Catherine Pawley, a patient recovering from anorexia. In this 8-minute video you will hear a brief overview of one person's experience with anorexia nervosa and will enhance understanding of the symptoms and emotional challenges associated with eating disorders. This video will also enhance understanding regarding the COLLECT and ASSESS part of the Patient Care Process.

INTRODUCTION

Eating disorders are widely accepted as serious mental illnesses. The spectrum of eating disorders encompasses several complex diseases, with most sharing the pathologic feature of overvaluation of body shape and weight. Eating disorders arise from the complex interaction between environmental, societal, developmental, psychosocial, genetic, and biologic factors. About 5 to 10 million females and 1 million males in the United States alone have an eating disorder. The urbanization of society, social pressure, and obsession with perfection and being thin have led to an increasing prevalence of eating disorders, with a median age of onset between 18 and 21 years, though estimates in adolescent studies suggest median ages of onset between 12 and 13 years.[1,2] Anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) are the most prevalent forms of eating disorders.[3]

1 Despite an improved understanding of these cognitively and emotionally disabling, and potentially fatal disorders, treatment remains difficult. Patients with eating disorders often demonstrate social difficulties prior to the onset of illness.[4] Pharmacologic intervention is a small part of a comprehensive treatment plan that emphasizes psychotherapy to address some of the social challenges, notably cognitive behavioral therapy (CBT) in adults and family therapy in younger patients.

EPIDEMIOLOGY

Anorexia Nervosa

Anorexia Nervosa (AN) impacts an estimated 0.9% to 2% of females in the United States. It usually presents during adolescent years (median onset 12.3 years of age) and 90% of the cases involve adolescents and young adults.[1,2] The estimated 12-month prevalence of the disorder in the general population is 0.4% of females with a smaller percentage in males.[2,3] Longitudinal management of AN is difficult, as patients are often resistant to weight restoration plans, and psychiatric comorbidities exist in over 50% of those with AN.[2] Rates of relapse requiring hospitalization within 1 year exceed 30%, and crude mortality rates are estimated at 15% for males and 5% for females.[5-7]

The promotion of the virtues of being thin is also a potentially negative environmental factor. Many "pro-anorexia" social media outlets inappropriately promote healthy lifestyle aspects of anorexia and being thin as a means of being in control and successful, while also serving as a means of support.[8]

Bulimia Nervosa

Bulimia nervosa (BN) usually presents in later adolescence or early adult life and similar to AN, 90% of cases are in adolescents a young adults.[2] Between 1% and 4.6% of adolescent and young adult females meet the diagnostic criteria for BN, with lifetime prevalence estimates of 1.5% in females and 0.5% in males.[1-3,9]

Binge-Eating Disorder

BED often presents in adolescence but can also emerge later in life.[3] Overall, BED is more common in females with a lifetime prevalence of 2% to 3.5% in adults and an approximate prevalence of 1% to 5% in adolescent-based studies utilizing the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*, see Chapter e81, "Evaluation of Psychiatric Illness") criteria.[10,11] The 12-month prevalence rate is an estimated 0.44%-1.6%.[12,13]

Other Specified and Unspecified Feeding and Eating Disorders

According to the *DSM-5*, additional diagnostic categories of specified and unspecified feeding and eating disorders exist where symptoms result in distress, but do not meet the full diagnostic criteria of specific feeding or eating disorders.[3] Examples listed within these categories include atypical AN, BN (lower frequency), BED (lower frequency), purging disorder, and night-eating syndrome (NES).[3]

NES is common in obesity clinic populations and is often accompanied by depressive symptoms. The syndrome is defined by repetitive night eating that includes eating after having been asleep or excessive food consumption following evening meals.[3,14] Night eating affects an estimated 1.5% of the general population with a high prevalence of obesity and psychiatric comorbidities.[15] Patients with NES are reported to benefit from antidepressant therapy, most notably sertraline 50 to 200 mg daily or escitalopram 5 to 20 mg daily.[14,15] Cognitive behavioral therapy may also be of benefit in NES, particularly in promoting weight loss.

Additionally, the *DSM-5* includes Pica, Avoidant/Restrictive Food Intake Disorder, and Rumination Disorder as stand-alone diagnoses within Feeding and Eating Disorders.[3]

ETIOLOGY

The exact etiology of eating disorders remains unknown and is likely multifactorial including genetic, biologic, developmental, and environmental mechanisms. While it is clear that brain reward mechanisms are altered, the exact biologic basis for eating disorders is difficult to delineate.

PATHOPHYSIOLOGY

Structural and functional brain imaging studies utilizing computed tomography (CT) and magnetic resonance imaging (MRI) have yielded a number of inconclusive findings. Anorexia nervosa has been linked with the development of enlarged cortical sulci, ventricles, interhemispheric fissure, and reductions in gray matter (amygdala, hippocampus, cingulate cortex, and putamen). Dystrophic abnormalities in the cerebrum have also been noted with weight loss, though normalization occurs with weight gain.[16] Abnormalities of the hypothalamic–pituitary–gonadal, hypothalamic–pituitary–adrenal, and hypothalamic–pituitary–thyroid axes are described as potential causes of AN. Amenorrhea is found in the majority of females with anorexia, providing support for the association with gonadotropin.[3,9]

Serotonin, norepinephrine, opioid, and dopamine neurotransmission and receptors have been studied extensively with varying roles in controlling eating behaviors. Special emphasis has been placed on the role of serotonin (5-HT), specifically noting reduced cerebrospinal fluid (CSF) basal concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of 5-HT, as well as increased binding of 5-HT1A receptors and reduced binding of 5-HT2A receptors in different regions within the central nervous system (CNS). Reduced dietary intake of tryptophan-containing foods leads to reduced levels of tryptophan, a requirement for 5-HT development.[17-19] 5-HT and dopamine function remain abnormal after weight restoration, with 5-HT activity being abnormally high in patients recovered from AN, while 5-HT2A receptors are reduced and dopamine receptors are increased following recovery.[18-20]

During acute phases of illness, BN and BED have been linked to hypoactivity of the frontostriatal circuits, abnormal amygdala response, diminished attentional capacity, and increased regional cerebral blood flow secondary to eating disorder-relevant stimuli.[21]

Complicating the study of these abnormalities is that their dysfunction is thought to be secondary to weight loss. Ghrelin, an amino-acid peptide produced by the stomach but centrally acting to promote food intake, is a current area of research focus.[22] Brain-derived neurotrophic factor (BDNF) is another protein of interest both eating and mood disorders.[20]

There are strong genetic influences in AN, and likely associations in both BN and BED as well. In addition, there is a high degree of premorbid anxiety and obsessive tendencies, which are also symptoms of disorders with suspected genetic associations. There is concordance of approximately 55% and 35% in monozygotic twins and 5% and 30% in dizygotic twins for AN and BN, respectively.

Genetic-based linkage studies offer hope for a future role of personalized medicine in eating disorder treatments, as numerous investigations have

examined predictors for developing AN. Studies to date have identified possible associations with chromosomes 1, 2, 3, 4, and 13; however, studies are limited by low sample size and results have not been consistent.[18,23,24] Some investigations have focused on polymorphisms of the 5-HT2A receptor and presence of low-function alleles associated with the 5-HT transporter (*5-HTTLPR, SLC6A4*) in combination of the 5-HT2A receptor gene (*–1438G/A*) suggest an association with poor treatment response.[25,26] Additional study has focused on the estrogen receptor I gene (ESRI) with the restrictive form of AN.[27] The polymorphism with the most significant association with BED to date is Taq1A.[28]

Emphasis is also placed on environmental factors such as social stress and psychological and developmental issues related to dysfunctional family relationships that may trigger abnormal eating behaviors. Athletes are at risk for eating disorders, include gymnasts, ballet dancers, figure skaters, distance runners, swimmers, wrestlers, and body builders.[29]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Anorexia Nervosa

General

- Restriction of energy intake that leads to low body weight and self-evaluation that is influenced by perceptions of weight and body shape

Symptoms

- Obsessions and fears about eating and gaining weight
- Complain about feeling full even when they have eaten very little food
- Denial of symptoms, failure to recognize low body weight, and low self-esteem
- Feelings of ineffectiveness and lack of self-control

Signs

- Weakness, lethargy, cachexia, amenorrhea, vomiting, restricted food intake, inappropriate exercise, delayed sexual development, edema, delayed gastric emptying, constipation, abdominal pain, bradycardia, hypotension, osteoporosis, dry cracking skin, lanugo, callus on dorsum of hand, cold intolerance, perioral dermatitis, and erosion of dental enamel

Laboratory Abnormalities

- Hypokalemia, hypochloremia, hypothyroidism, hypophosphatemia, hypokalemic alkalosis, hypomagnesemia, metabolic acidosis, blood urea nitrogen, hepatic enzymes, leukopenia, thrombocytopenia, anemia, QT interval prolongation, bradycardia, hypercholesterolemia, and bone mineral density

Other Diagnostic Tests

- Nonspecific electroencephalogram (EEG) changes

CLINICAL PRESENTATION: Bulimia Nervosa

General

- Binge-eat which stops with abdominal pain or self-induced vomiting or interruption by another person
- Pattern of severe dieting followed by binge-eating episodes
- Concerned about body image but do not have the drive to thinness, which is a characteristic of AN

Symptoms

- Do not eat regular meals and do not feel satiety at the end of a meal
- May use purging methods such as laxatives for weight control
- Feelings of guilt, depression, and self-disparagement after binges
- Social isolation can result from frequent bingeing
- Chaotic and troubled personal relationships and substance use are common

Signs

- Bingeing, vomiting, salivary gland inflammation, erosion of dental enamel, callus on dorsum of hand, perioral dermatitis, dental caries, parotid gland enlargement, abdominal pain, upper end of normal body weight or slightly overweight, frequent weight fluctuations, and diminished masticatory ability

Laboratory Abnormalities

- Hypokalemia, hypochloremic metabolic acidosis, and elevated serum amylase

Other Diagnostic Tests

- None

CLINICAL PRESENTATION: Binge-Eating Disorder

General

- Repeated episodes of binge-eating that includes a lack of self-control and eating an amount of food that is beyond what most people would eat
- Episodes of binge-eating may include rapid eating, a sense of fullness to the point of being uncomfortable, eating when not hungry, eating alone secondary to feeling embarrassed, and a sense of self-disgust, depression, or guilt

Symptoms

- Episodes of binge-eating
- Lack of self-control
- Rapid consumption of food
- Feeling full and eating when not hungry
- Isolation and guilt/depression

Signs

- Obesity
- History of weight loss followed by weight gain
- Binge-eating without compensatory purging
- Comorbid psychiatric (eg, depression, anxiety, ADHD, insomnia) and medical complications (eg, GERD, hypertension, pain disorders, dyslipidemia, and asthma)

Laboratory Abnormalities

- Elevated lipids, glucose, and hemoglobin A1C, abnormal electrolytes, and increased weight

Other Diagnostic Tests

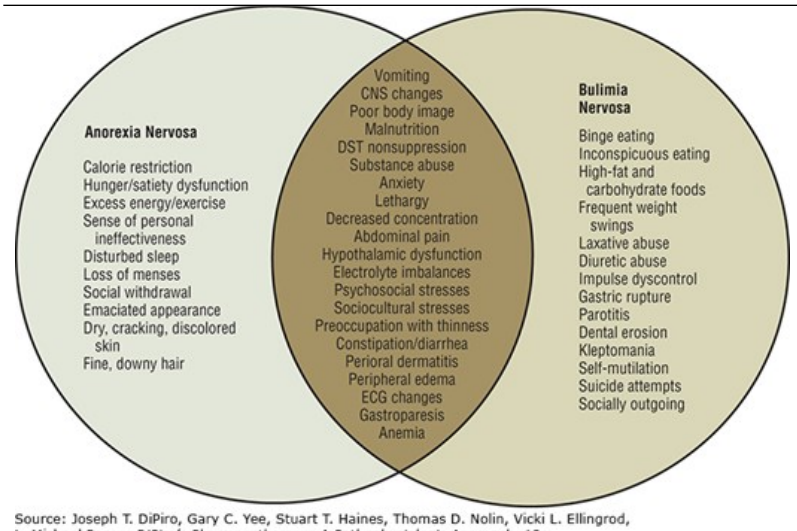
- None

2 Symptoms common to all eating disorders include excessive intake of calorie-laden food over a short period of time (eg, binge eating or bingeing), and inappropriate compensatory behaviors to expend calories such as self-induced vomiting, the overuse of laxatives, diuretics, enemas, fasting, or excessive exercise (eg, purging behaviors).

3 Anorexia nervosa and BN occur together in ~30% to 64% of patients with eating disorders, thus appearing as a continuum of symptoms making careful medical and psychiatric assessment at baseline essential.[30] Patients who initially present with either AN or BN may alternate from one disorder to the other, especially in cases where remission is not achieved. Figure e83-1 demonstrates similar and unique features of both disorders. Adolescent and adult males may present with body image concerns skewed toward mascularity.[31]

FIGURE e83-1

Signs and symptoms of anorexia nervosa and bulimia nervosa. (DST, dexamethasone suppression test; ECG, electrocardiogram)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The use of purging methods is not limited to BN and self-induced vomiting is the most common form of purging behavior.[32] Laxative overuse is another form of purging common in both AN and BN, used by an estimated 3% to 70% of patients.[32-34] Although ineffective as a weight-loss strategy, laxative overuse is often done in combination with other behaviors, including exercise, diuretics, enemas, and saunas. Within the diagnostic framework of AN, laxative overuse is most common in those identified with the purging subtype.[32] Psychiatric symptoms of depression, anxiety, and borderline personality disorder are also reported in those who overuse laxatives.[32-34]

Depression, schizophrenia, obsessive-compulsive disorder (OCD), and conversion disorders should be included in the differential diagnosis of AN, BN, and BED as eating abnormalities can be a component or share similar symptoms of these illnesses. The salient differences are the overriding drive for thinness, disturbed body image, increased energy directed at losing weight, and binge-eating episodes that are relatively specific for eating disorders. Most patients with eating disorders experience relief of psychiatric symptoms on refeeding.[35]

Anorexia Nervosa

The presentation of AN includes a recent period of weight loss and associated behaviors to promote this weight loss, such as vomiting, limiting food intake, and excessive exercise. Current diagnostic criteria for AN include the restriction of energy intake relative to requirements, which leads to low body weight contextually as it relates to age, sex, developmental trajectory, and physical health.[3] The *DSM-5* further classifies AN as restricting type in which patients restrict food intake with no binge-eating or purging behavior over the past 3 months, or binge-eating/purging type, in which patients regularly participate in bingeing or purging over the prior 3 months.[3] The severity of AN is based upon body mass index (BMI) in adults and BMI percentiles in children and adolescents. Comorbid psychiatric conditions, such as major depression, are frequent but should initially be considered secondary to starvation and not a true mood disorder. Specific risk factors for AN include female sex, having a sibling with AN, the presence of mood disorders in family members, and comorbid anxiety, personality, or substance use disorders.[36]

4 Psychiatric comorbidity is common, as up to 75% of patients have a primary mood disorder, and there is also an association with personality disorders and anxiety disorders, such as social phobia and OCD.[2,37] The lifetime prevalence of OCD in patients with AN is reported to be as high as 40% compared to 2.5% in the general population.[37-39] The impact that psychiatric comorbidity has on treatment outcomes of AN is unknown, but it is important to understand that deprivation of food may contribute to both mood and cognitive fluctuations.

Bulimia Nervosa

The core feature of BN is recurrent episodes of binge-eating. Most patients with BN have normal weight, although they might fluctuate between being underweight and overweight. Patients lack control over their eating and participate in recurrent compensatory behavior to prevent weight gain. These behaviors may include self-induced vomiting; overuse of laxatives, diuretics, enemas, or other medications; strict dieting or fasting; or excessive exercise. To meet *DSM-5* criteria, the binges and compensatory behaviors must occur on average at least once weekly for 3 months.[3] Bulimia nervosa

can further be differentiated by purging type (regularly engages in self-induced vomiting or the overuse of laxatives, diuretics, or enemas) or non-purging type (uses other inappropriate compensatory behaviors, such as fasting or excessive exercise, but does not engage in purging activities).[3]

Patients with BN typically binge and vomit at least once daily. Caloric intake varies, but patients can consume between 5,000 and 20,000 cal (20,900 and 83,700 J) during a single binge and they tend to consume foods that are easy to ingest, do not require much chewing or preparation, and are high in carbohydrates or fat. Binge-eating is typically secretive and precipitated by a stressful event, followed by post-binge remorse. In general, binges often last less than 2 hours but can extend to more than 8 hours. To compensate for the excessive caloric intake, many patients fast for prolonged periods, exercise compulsively, purge, or overuse laxatives.

Psychiatric comorbidity for BN includes depression (up to 80%), poor impulse control, and substance use. Approximately 30% to 37% of patients diagnosed with BN have a personal history of substance use.[40] Kleptomania and borderline and avoidant personality disorders are also frequently observed, as patients also commonly steal laxatives and comfort items, such as candies and clothes.[9,37,41]

Binge-Eating Disorder

Patients with BED present with recurrent episodes of bingeing without the maladaptive compensatory behaviors with approximately half of patients seeking treatment.About 5% to 10% of patients seeking treatment for obesity have BED.[42] Comorbid psychiatric disorders are reported in greater than 70% of BED patients with depression and low self-esteem seen most commonly. The self-deprecating focus on body image possible with BED is less severe than in AN or BN.[39,43] Diagnostic criteria for BED requires recurrent episodes of binge-eating (eating an amount of food in a 2 hour time frame that is larger than what most people would eat in a similar situation and a sense of lack of control over eating during the episode).[3] The binge-eating episodes are associated with at least three of the following: eating more rapidly than normal; eating until feeling uncomfortably full; eating large amounts of food when not physically hungry; eating alone because of embarrassment of how much is being eaten; and feeling disgusted with oneself, depressed, or guilty after the episode. The severity of BED is determined by the number of binge-eating episodes per week (1-3 = mild; 4-7 = moderate; 8-13 = severe; 14 or more = extreme).[3]

Medical Complications of Eating Disorders

5 The potential medical complications of eating disorders involve multiple organ systems. The type of medical complication encountered is dependent on the type and frequency of the eating disorder behavior. Cardiac complications may occur and can include arrhythmias such as sinus bradycardia, cardiac muscle atrophy, orthostatic hypotension, decreased cardiac output, arrhythmia, and QTc interval prolongation.[44,45] During caloric restoration, there is a potential risk for developing refeeding syndrome, which can progress to fatal cardiovascular collapse. This risk is reduced by the gradual versus rapid reintroduction of calories.

Metabolic (eg, metabolic acidosis and metabolic alkalosis) and electrolyte disturbances (eg, hypokalemia, hypomagnesemia, and hypocalcemia) and dehydration are often seen. Elevations in bicarbonate levels during periods of hypokalemia can be an indication that the patient is inducing vomiting or using dietary weight-loss medications. Non-anion-gap acidosis has also been reported with the overuse of laxative agents. Additionally, both acute and chronic renal failures have been reported.

Gastrointestinal (GI), oropharyngeal, and dental complications are frequent, as are general complaints of lethargy and fatigue. Evidence of Russell's sign may be present, which is signified by skin lesions on the fingers used to induce vomiting.

Hormonal changes related to the hypothalamic–pituitary–gonadal axis resulting from starvation are often seen. These abnormalities include effects on estradiol, the gonadotropins (eg, luteinizing hormone, follicle-stimulating hormone, and gonadotropin-releasing hormone), thyroid function, adrenal function, and growth hormone.[9,44] A syndrome has been identified in female athletes and termed the "female athlete triad," defined by the development of irregular menses, osteoporosis/low bone mineral density (BMD), and disordered eating.[44,46] An athlete may experience only one or two components of the triad, or all three.[47] Because low BMD and abnormalities in hormone levels is not gender specific, the term "relative energy deficiency in sport" has been recommended to replace the "female athlete triad" designation to represent the syndrome in both female and male athletes.[48] Osteopenia and osteoporosis are potential long-term complications of suppressed estrogen. The restoration of weight, specifically in AN, reverses the bone loss, although estrogen supplementation does not appear to be effective.[49] In all cases, the preferred method to address these

issues is the normalization of nutrition. The impact on female fertility is not well studied, although the ability to carry a pregnancy to term or to give birth to a child of average birth weight appears reduced.

Chronic starvation can contribute to brain atrophy; however, decreases in white matter and CSF volumes return to normal after a healthy weight is achieved, but gray matter loss can persist.[35,50,51]

Obesity is common in patients with BED and may also be present in patients with BN, placing these patients at an increased risk of medical comorbidities including type 2 diabetes mellitus, dyslipidemia, and hypertension.[30] Assessment should include measurement of weight, height, pulse rate, blood pressure, and calculation of BMI. Random glucose and ECG should be done as medically indicated.[30]

A thorough physical and laboratory evaluation, as described in Table e83-1, is essential to determine the severity of medical complications.[3,30,35,51]

TABLE e83-1

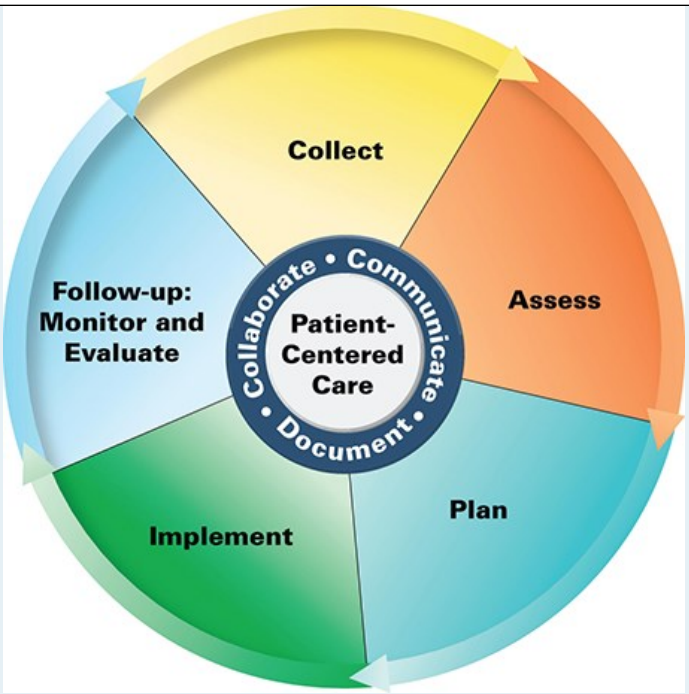
Physical and Laboratory Assessment of Eating Disorders

Evaluation	Target Symptoms
Pulse	Bradycardia, tachycardia
Blood pressure	Hypotension, orthostasis
Height/weight	Underweight for size and age/body mass index
Respiratory rate	Rapid if heart failure occurs during refeeding
Temperature	Hypothermia, cold intolerance
Electrocardiogram	ST depression, flat T waves, U waves, increased QT interval, atrioventricular block
Gastrointestinal	Hypoactive bowel sounds, gastritis, abdominal distention
Skin	Dryness, scaling, lanugo, hair loss, calluses on fingers and hands
Menses	Amenorrhea
Complete blood count	Leukopenia, anemias, thrombocytopenia
Electrolytes	Hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, or hyperphosphatemia
pH	Metabolic alkalosis (acidosis if laxative overuse)
Amylase	Elevated; pancreatitis rare
Liver	Hypoalbuminemia, elevated γ-glutamyl transferase if alcohol misuse, elevated AST
Thyroid	Low to low normal, but not true thyroid disease
Cortisol	Elevated with lack of suppression on dexamethasone suppression test
Bone density	Osteoporosis, osteopenia
Renal	Reduced eGFR (less than 60 mL/min/1.73 m^2)
Endocrine	Hypoglycemia

Data from References 3,9,30,46-49,52.

PATIENT CARE PROCESS

Patient Care Process for Eating Disorders



Collect

- Patient characteristics (eg, age, race, sex, gender identity, pregnancy status)
- Patient history (past medical, family, social—dietary habits, exercise patterns, laxative use)
- Weight history and body mass index (BMI)
- Current medications and prior eating disorder treatment(s)
- Objective data
  - Blood pressure (BP), heart rate (HR), height, weight, and BMI
  - Labs (eg, serum electrolytes, serum creatinine [Scr], estimated glomerular filtration rate [eGFR], blood urea nitrogen [BUN], metabolic panel)
  - Other diagnostic tests when indicated (eg, ECG, EEG, bone mineral density)

Assess

- Symptoms of eating disorders (eg, anorexia nervosa, bulimia nervosa, and binge-eating disorder) that may include poor body image, weight change, lethargy, binging, purging, and GI complaints (Tables e83-1 and 83-2)
- Presence of mental health conditions (eg, depression, schizophrenia, anxiety disorders)
- Presence of medical conditions (eg, malnourishment, cardiac arrhythmia, refeeding syndrome, metabolic acidosis and alkalosis, dehydration, GI complications, osteopenia, osteoporosis, dental problems) (Fig. e83-1)
- Laboratory abnormalities (eg, hypokalemia, hypothyroidism, hypomagnesemia, hypophosphatemia) (Table e83-1)
- Current medications that may exacerbate eating disorder symptoms (eg, diuretics, laxatives)
- For the type of eating disorder identified, assess the appropriateness of medication therapy (see “Treatment” section)

Plan*

- Nonpharmacologic treatments (eg, nutritional rehab, education, and counseling; cognitive behavioral therapy; interpersonal psychotherapy; dialectical behavior therapy, family, and/or group therapy) (see "Treatment" section)
- Pharmacotherapy dependent upon the eating disorder identified (eg, antidepressants, antipsychotics, antiseizure medications, lisdexamfetamine) (see Fig. e83-2)
- Monitoring parameters including efficacy (eg, BP, cardiovascular events, kidney health), safety (medication-specific adverse effects), and time frame
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, pharmacotherapy)
- Self-monitoring of weight, BMI, BP, and HR—where and how to record results
- Referrals to other providers when appropriate (eg, physician, dietitian)

Implement*

- Provide patient education regarding all elements of treatment plan (nonpharmacologic and pharmacologic)
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up assessments of treatment

Follow-Up: Monitor and Evaluate*

- Changes in eating habits and compensatory behaviors (Fig. e83-1)
- Weight, vital signs, and laboratory values (Table e83-1)
- Psychiatric (mental status examination) and physical condition stability
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

Desired Outcomes

The goals for patients with eating disorders are to reduce distorted body image; restore and maintain healthy body weight; establish normal eating patterns; improve psychological, psychosocial, and physical problems; resolve contributory family problems; enhance adherence; and prevent relapse.[32] Specific to BED is the additional goal of weight loss, if applicable.

Anorexia Nervosa

6 The long-term prognosis of patients with AN is not clear, as the majority of studies focus on acute treatment. The course of the disorder most commonly consists of a single episode with subsequent return to normal weight, although patients can still experience issues with disturbed body image, disordered eating, and other psychiatric problems after weight has normalized.[35] Some patients experience an unremitting course leading to death, whereas others suffer episodically. Remission rates improve with longer treatment times, as the lowest rates are reported in shorter-duration follow-up trials, while remission rates near 80% have been reported in longer-term follow-up studies at 8 and 16 years.[53] Up to 20% of patients remain chronically ill despite weight normalization, return of menses, and improved eating behaviors.[54] Long-term prognosis is more favorable with extended

follow-up care and younger age at onset, whereas a poorer prognosis is associated with chronic illness, lower initial weight, poor family relationships, obsessive-compulsive personality symptoms, and the presence of bulimia or purging behavior.[25,54,55] Crude mortality rates appear to be lower than historically projected with the estimated mortality rate being 2.8% to 4%. When death occurs, it is most often the result of cardiac arrest or suicide.[3,53,54]

Bulimia Nervosa

The prognosis of BN appears to be more favorable than that of AN. Patients with milder presenting symptoms who are treated as outpatients tend to do better, whereas those with electrolyte imbalances, esophagitis, dental caries, and salivary gland enlargement have a more complicated course.[9] The presence of psychiatric comorbidity and greater general psychiatric symptom severity has been determined to be poor prognostic indicators. Longer rates of follow-up tend to have higher rates of remission, reaching 70% or higher with 5 to 20 years of follow-up. However, even in cases in which patients respond, they continue to exhibit symptoms that wax and wane, sometimes meeting full criteria for diagnosis of BN or subthreshold forms of BN that do not meet full criteria. Total absence of symptoms is an uncommon outcome, and residual symptoms predispose disease relapse.[53] The actual definition of recovery varies, as once-a-month binge–purge episodes are considered by some to be recovery, if their episodes were previously more frequent, whereas other clinicians consider a patient recovered only when there is complete absence of these behaviors.[56]

Binge-Eating Disorder

Studies to date suggest higher remission rates (25%-80%) in 1- and 4-year follow-up studies compared with findings in AN and BN longitudinal studies. These numbers are irrespective of selected treatment. Although sex is not a significant treatment outcome moderator, males generally have lower psychopathology and lose more weight over the course of treatment.[57] Estimated crude mortality rates range from 0% to 4.7% with a cumulative mortality rate reported at 0.5%.[53,58]

General Approach to Treatment

Treatment plans are individualized based on the severity of specific core features of the eating disorder and comorbid medical and psychiatric conditions. The absence of an adequate support system of family and friends can contribute to failed treatment. A critical first step is to determine illness severity, as that drives both the intensity and the setting for delivery of care. Hospitalization is generally reserved for the most severely ill patients. In AN, lower admission BMI and the presence of purging symptoms and austerity predict longer lengths of stay.[59] Some criteria for hospitalization are outlined in Table e83-2.[3,29,35,60] Medications are part of the comprehensive treatment strategy for eating disorders, but are rarely recommended as the sole treatment.[61-63] Comparative, double-blind, placebo-controlled trials are sparse, and most are limited by small sample sizes and high dropout rates. Additionally ambivalent patient attitudes toward treatment, and medical complications complicate interpretation of these studies.[64]

TABLE e83-2

Considerations for Hospitalization of Patients with Eating Disorders

- Rapid weight loss or Body Mass Index (BMI) less than 12
- Reduced oral intake of food (sudden and persistent)
- Medical complications (eg, edema) and metabolic abnormalities (eg, hypoproteinemia) from bingeing, purging, and starvation (eg, heart rate less than 40 beats/min, heart rate greater than 120 beats/min, blood pressure less than 90/60 mm Hg, glucose less than 60 mg/dL [3.3 mmol/L], potassium less than 3 mEq/L [3mmol/L], or inability to maintain core temperature)
- Co-occurring psychiatric symptoms, notably suicidal ideation, self-harm, psychotic depression, or substance use disorder
- Nonresponsive to outpatient treatment (after 3-4 months) and poor motivation to recover
- Demoralization or nonfunctional family
- Denial of severity of abnormal eating behaviors
- Continuous supervision required to prevent purging (eg, vomiting or laxative overuse)

Data from References 3,25,29,31 and 60.

Anorexia Nervosa

Nonpharmacologic Therapy

7 Evidence supports psychotherapy-based treatments have the greatest likelihood of eliciting a response in patients with AN.[30,35,60,65] However, the specific type of psychotherapy that is preferred varies and may include CBT, dialectical behavioral therapy (DBT), focal psychodynamic therapy, acceptance and commitment therapy, behavioral management, specialist supportive clinical management, interpersonal psychotherapy, nutritional counseling, exposure and response prevention, and family therapy.[30,35,37,52,60,65,66] In younger patients, family therapy is the preferred first-line therapy and focuses on re-establishing parental control, promoting wellness, and utilizing other family members for support.[67] Improved outcomes have been seen in patients of a younger age, a shorter duration of illness, a restrictive type AN, being employed, lack of psychiatric co-morbidity, and better social adjustment.[65] Current guidelines suggest at least 6 months of psychotherapy is preferred, though studies of at least 1 year in duration have demonstrated favorable outcomes by reducing relapse rates.[30,60,68] Overall, CBT helps patients overcome distorted thinking, including self-worth as measured by body image, feelings of being fat despite evidence to the contrary, and denial. Additionally CBT teaches how to use strategies besides eating to cope.

Interpersonal psychotherapy focuses on interpersonal relationships and functioning, whereas CBT provides positive reinforcement for weight gain.[38] A combined approach of interpersonal psychotherapy and CBT is a reasonable treatment approach.[37] Initial treatment is directed toward restoring a healthy weight, especially in inpatient settings where target weights are often more rapidly achieved.[37] Many psychiatric symptoms in an acutely ill patient, such as depression and anxiety, diminish or disappear with weight restoration. After medical stability and appropriate weight are reached, therapy can be redirected toward addressing ongoing interpersonal problems, weight maintenance, cognitive restructuring, and skill development for relapse prevention.[30]

Oral refeeding, initially with liquid formulas if necessary, is the most common approach to weight restoration. In severe cases when a patient refuses to eat, nasogastric refeeding is preferred over intravenous bolus dosing in part because it can allow for higher initial caloric intake and has been associated with reductions in length of inpatient hospitalizations and increased rate of weight gain without an increase in complications.[69] Total parenteral nutrition is reserved only for the management of severely malnourished patients and if other refeeding methods fail. The decision to administer total parenteral nutrition must be made carefully, because of the potentially devastating psychological effect on patients who do not wish to gain weight.

Current clinical evidence suggests a controlled weight gain of 0.9 to 1.4 kg (2-3 lb) per week in inpatient settings and 0.2 to 0.5 kg (0.5-1.1 lb) per week in

outpatient settings.[3,63,70] Refeeding recommendations vary between younger patients and adults and are considered controversial. An acceptable approach for younger patients is to begin refeeding at 800 to 1,000 cal/day (3,300-4,200 J/day), while others suggest a more aggressive approach.[71] Adults may be considered for refeeding initiation in the range of 1,000 to 1,600 cal/day (4,200-6,700 J/day) (30-40 cal/kg/day [130-170 J/kg/day]) with slow titration (every other day) upward (100-200 cal/day [420-840 J/day]) until they begin to demonstrate sustained weight gain or achieve target weights.[35,60,72] This can require the intake of an additional 3,500 to 7,000 cal (14,600-29,300 J) per week.[60] Slow refeeding has long been considered important to prevent psychological and medical consequences, including the potentially fatal severe electrolyte disturbance that results from insulin surges known as refeeding syndrome. However, too conservative of an approach results in further weight loss early in treatment (unfeeding syndrome), which contributes failure in achieving nutritional recovery goals.[73]

Pharmacologic Therapy

Antidepressants

Studies have examined the role of antidepressants in the treatment of AN, but are limited by small sample sizes and large confidence intervals. Concurrent major depressive disorder has been associated with longer AN associated hospitalizations and fewer patients achieving weight restoring and caloric intake goals.[74] Antidepressants currently have no role in the acute treatment of AN, unless there is another clinical indication present.[25,35,61]

Pharmacotherapy may be ineffective, especially in cases where the patient is below their expected weight. Thus, antidepressants should be initiated only if depression, anxiety, obsessions, or compulsions persist after the target weight is achieved.[25,70] The duration of treatment is unclear, but one study showed benefit in patients treated for 1 year, and current guidelines suggest 9 to 12 months of therapy.[30,35,60,65,68] Antidepressants, along with psychotherapy, have been used to help maintain weight and prevent relapse, but data supporting this are limited. Most clinicians prefer the selective serotonin reuptake inhibitor (SSRI) antidepressants because they are better tolerated and have greater cardiovascular safety than tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[30,35,65,68] Because these patients are sensitive to anticholinergic and cardiovascular effects, low starting doses and slow titration toward an effective dose are appropriate if a TCA or MAOI are used. The risk of cardiotoxicity in a malnourished population must not be underestimated, and a baseline electrocardiogram (ECG) should be obtained before initiation of these agents. Chapter 88, “Depressive Disorders,” contains a list of common adverse effects seen with antidepressant use.

Fluoxetine is the most widely studied SSRI in AN. Most clinicians initiate at low doses (eg, 20 mg/day), and increase to a maximum of 60 mg/day based on response and tolerability.[72,73,75] Controversy exists regarding when antidepressant therapy should be initiated. Antidepressants may be ineffective during the starvation phase of anorexia, partly due to reduced tryptophan levels. Debate remains as to their effectiveness once weight restoration has occurred. Evidence from a 52-week, randomized, placebo-controlled clinical trial which included fluoxteine doses from 20 to 80 mg/day after weight restoration showed no difference for time to relapse.[76] In addition, the greatest risk of relapse appears to be within the first 60 days after discharge to outpatient care.[77]

Antipsychotics

First- and second-generation antipsychotics have been utilized as a treatment for AN, specifically targeting anxiety and obsessive and paranoid thoughts related to weight gain. First-generation antipsychotics contribute to BMI gains, but provide little benefit overall at reducing other core symptoms, and their associated adverse events outweigh the benefits. Second-generation antipsychotics have provided an additional alternative for treating AN, with reports of improvement in weight gain and reductions in symptoms such as depression, anxiety, and obsessive-compulsiveness. Most of the data are from case reports or small trials in both adolescents and adults using risperidone 0.5 to 2.5 mg daily, olanzapine 2.5 to 10 mg daily, and quetiapine 50 to 800 mg daily.[76,78-82] In addition, an outpatient study examining olanzapine versus placebo, independent of concurrent psychotherapy, demonstrated significant improvement in rate of weight gain and achieved a higher BMI, though there was no difference in obsessive behaviors.[83] Despite these reported benefits, a meta-analytic review of second-generation antipsychotics that included olanzapine, quetiapine, and risperidone did not find significant differences in BMI gains or eating disorder psychometric outcome assessments.[84]

Optimal treatment duration is unknown, as most of the larger studies are less than or equal to 3 months in duration. Chapter 87, “Schizophrenia,” contains a list of common adverse effects seen with antipsychotic use.

Miscellaneous Agents

Metoclopramide can be helpful in reducing bloating, early satiety, and abdominal pain commonly found in AN, but it does not affect weight gain.[35] Low-dose, short-acting benzodiazepines (eg, 0.25 mg alprazolam or 0.5 mg lorazepam) given before meals are useful when severe anxiety limits eating.[35] Estrogen replacement has been used, but restoring menses through refeeding is the preferred approach to minimize bone density loss. Supplementation with zinc is also being studied to assist with weight restoration.[65]

Combination Therapy

The combination of psychotherapy and pharmacotherapy, while routinely done in practice, lacks randomized, placebo-controlled, blinded studies to support outcome difference compared to either treatment approach alone. Fluoxetine and olanzapine have each been studied in combination with behavioral or cognitive-behavioral therapy within inpatient and outpatient settings. Only one study that combined a day-hospital program with olanzapine demonstrated significant benefit with weight restoration, achieving the target BMI, and reducing obsessive symptoms.[81]

Bulimia Nervosa

Nonpharmacologic Therapy

Outpatient-based treatment is most often recommended except in extreme cases (see Table e83-2). The nondrug strategies used in BN are similar to those used with AN, and they are equally critical to success. Overall, CBT has the strongest evidence supporting its benefit in managing BN.[30,60,65,85] According to treatment guidelines CBT should consist of 16 to 20 sessions over a 4- to 5-month period.[30,60] Thirty percent to 50% of individuals who receive CBT for BN may be abstinent from binge-eating and purging behaviors by conclusion of the treatment.[86] Interpersonal psychotherapy also plays a role and has a moderate degree of evidence to support its use, but it is considered less effective than CBT.[35] CBT is considered more effective at reducing bingeing and purging episodes than psychoanalytic psychotherapy and also faster at alleviating eating disorder features and general psychopathology. Psychodynamic therapy as well as family-based therapy are also viable options for treatment of adolescents with BN.[86] Nutritional counseling, planned meals, especially regular consumption of evening meals, and self-monitoring can help interrupt the binge–purge cycle.[87] Programs using motivational teaching and guided CBT-based self-help programs which target mechanisms such as dietary restraint and shape and weight concerns have shown promise.[38,85,88-90] When such programs have been combined with medication (eg, fluoxetine), enhanced response has been reported. Online delivery of CBT and web-based aftercare may provide an acceptable treatment alternative for patients who have limited access.[91] Data support the use of 12-step programs, but they should not be used as monotherapy.[25,35] Additional nonpharmacologic strategies may include the promotion of aerobic exercise, yoga, massage therapy, and body awareness therapy.

Pharmacologic Therapy

Antidepressants

Antidepressants are often used in the acute and maintenance phases of BN adjunctively with nonpharmacologic approaches. Most evidence-based guidelines consistently recommend antidepressants, specifically fluoxetine, in combination with psychotherapy.[93] A wide array of antidepressants, including TCAs, MAOIs, trazodone, serotonin–norepinephrine reuptake inhibitors (SNRIs), bupropion, and SSRIs, have been studied. Additionally, several reviews analyzing this body of literature have been published, although there continues to be limited placebo-controlled, randomized, double-blind clinical studies.[23,61,85,94] Antidepressants are reported to reduce depression, anxiety, obsessions, and impulsive behaviors, such as binge-eating and purging, and improve eating habits, although their impact on body dissatisfaction remains unclear. The presence of comorbid mood disorders is not necessary for a response in patients with BN.

Their benefit appears to be more robust in the acute phase of the illness, as relapse despite continued antidepressant use is common in patients who are in or near remission.[25,63] Antidepressant response usually occurs in 6 to 8 weeks, and reduction in frequency of binge–purge behavior ranges from 0% to 73%.[61] Abstinence rates (eg, elimination of bingeing and purging behaviors) with short-term use range from 0% to 68%. More data are needed to determine the long-term benefits of antidepressants for preventing relapse of bulimia symptoms. One trial evaluating the impact of fluoxetine versus

placebo in the maintenance phase showed a better outcome in patients receiving fluoxetine 60 mg daily, although high dropout rates in both groups blurred the overall benefit.[95]

SSRIs are the preferred agents because of their tolerability and because they have been studied in the largest number of patients. Fluoxetine remains the only medication with FDA approval for BN in adults. While it is not approved for pediatric BN, fluoxetine is FDA approved for child and adolescent depression and obsessive-compulsive disorder, making it a reasonable option if pharmacologic treatment of BN is considered in pediatric patients.[96] Efficacy of other SSRI agents is still lacking, but an alternative SSRI may be considered in clinical practice for those not responding to fluoxetine.[94] Tolerability is the primary criterion for selecting an antidepressant in the treatment of BN because of patients' heightened sensitivity to adverse effects and the lack of a clear difference in efficacy between the classes. Even though there is a suggestion that MAOIs produce the most robust effect, the risk of using these medications in impulsive patients limits their use.[63] SNRIs have shown promising results; however, the data supporting their use are limited to case reports. Bupropion, a norepinephrine–dopamine reuptake inhibitor, is contraindicated in patients diagnosed with BN because of the increased risk of seizures seen in patients with an eating disorder.

Before initiating pharmacologic therapy, a careful baseline physical examination, ECG, and laboratory workup are essential. Underlying ECG changes secondary to hypokalemia or bradycardia and atrioventricular block from starvation can be present. There is potential for fatal outcomes secondary to cardiac arrest or suicide. All antidepressants can cause seizures; thus, a careful risk–benefit assessment is warranted if the patient has predisposing factors such as a personal or family history of seizures, cerebrovascular disease, or alcohol or sedative–hypnotic withdrawal.

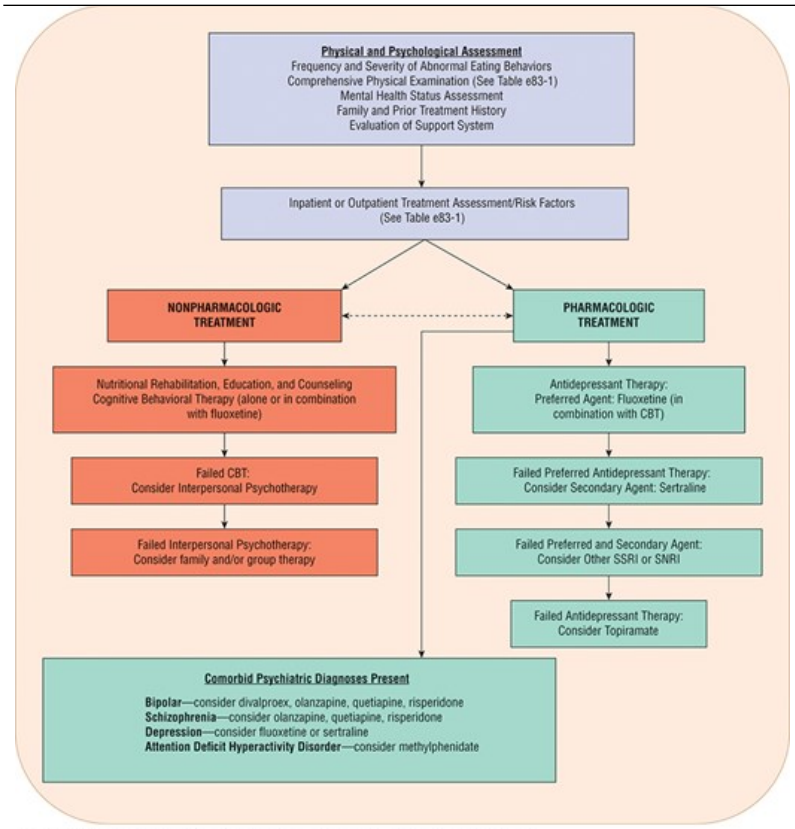
Doses in the treatment of BN are similar to those used for depression, although at the higher end of the range. Chapter 88 includes antidepressant dosing ranges, of note, fluoxetine 60 mg daily can be necessary for response.[97] With all agents, most clinicians initially target the bottom to the middle of the dosing range and increase the dose if there is an inadequate response. Slow titration is needed to allow for tolerance to adverse effects. If TCAs are used, serum concentration monitoring is recommended to ensure that absorption is not compromised by purging.

The time for antidepressant onset of effect in BN is unclear. In the absence of data, the definition of a therapeutic trial from the depression literature (eg, 4-8 weeks at a therapeutic dose) should be used. Response (eg, defined as greater than 60% reduction in binge-eating or vomiting frequency) by week 3 is a positive predictor of eventual treatment response.[98] Because the majority of subjects will not experience a complete remission, and data regarding predictors of response or the impact of switching to another class are not available, clear and specific treatment outcomes should be stated initially.[19]

Optimal duration of treatment after response is poorly defined, although most clinicians treat for 9 months to 1 year and then reevaluate. The evidence is mixed as to whether any early benefit is sustained; hence, the decision to continue treatment should be made based on both initial response and the maintenance of that benefit. If the symptoms return within a few months after antidepressant discontinuation, then the treatment may need to be reinitiated. Figure e83-2 describes criteria for medication use in BN.

FIGURE e83-2

Bulimia nervosa treatment algorithm. (CBT, cognitive behavioral therapy; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor)



Miscellaneous Agents

Due to lack of evidence demonstrating their benefit, lithium and traditional antiseizure medications are reserved for patients diagnosed with BN and comorbid bipolar disorder.[35,99] Randomized, placebo-controlled trials with topiramate have demonstrated reduced binge/purge frequency and weight loss versus placebo, although adverse effects including cognitive impairment and paresthesia may hinder medication adherence.[100,101] Low-dose benzodiazepines before meals can help reduce anxiety associated with refeeding, although long-term use is not warranted because of the risk of dependence. One double-blind trial with ondansetron has shown benefit, but there are insufficient data to recommend a specific role for this agent.[102] One small, open-label, pilot study of zonisamide showed it to be effective in BN, but further data are needed to confirm its role in treatment.[103] Data are conflicting on the opiate antagonist naltrexone with only modest improvement seen at high doses, but it is not recommended due to risk of elevated hepatic transaminases.[78] Antipsychotics and appetite suppressants do not play a role in managing core symptoms of BN.[25]

Combination Therapy

The combination of pharmacologic and nonpharmacologic measures appears to produce the best chance for positive outcomes for patients with BN. However, a recent review of randomized controlled trials suggested no added benefit.[60,104] Antidepressants, specifically SSRIs, are the medications of choice in patients diagnosed with BN, whereas other medications are reserved for patients with comorbid psychiatric conditions. Only in unusual circumstances should patients be treated with antidepressants alone. The greatest benefit of SSRI use is during the acute phase of treatment, whereas data are mixed regarding their role in the prevention of relapse.

Binge-Eating Disorder

Nonpharmacologic Therapy

CBT is universally accepted as the nonpharmacologic treatment intervention of choice, specifically aimed at reducing the number binge-eating

episodes that results in a remission rate of approximately 50%.[105,106] Evidence supports individual, group, and guided self-help are efficacious. In general, interpersonal psychotherapy (IPT) has demonstrated comparable efficacy to CBT at 1-, 2-, and 5-year follow-up reviews, with DBT and mindfulness also being appropriate psychotherapy treatment interventions, though not considered first-line.[107,108] These interventions have been shown to improve long-term remission rates.[109] Improvements in impulse control and cue reactivity should be included as a target of psychotherapeutic interventions.[110,111] Behavioral weight loss programs typically produce a 5% to 10% weight loss which is often regained in the subsequent 1 to 2 years.[102] Sustained weight loss has been more favorably associated with CBT.[105,109,112] Physical activity used in conjunction with CBT and a dietary program has resulted in improvement of both binge episodes and BMI. Other innovative treatments of interest include cue-exposure therapy, virtual reality, tele-delivery of services, and the ketogenic diet.[110,113]

Pharmacologic Therapy

9 Lisdexamfetamine, antidepressants, and antiseizure medications are the pharmacologic agents most extensively studied in BED. Antidepressants have demonstrated efficacy as monotherapy at reducing binge-eating and improving depressed mood during the acute phases of the illness compared with placebo.[30,78,111,114-116] The SSRIs citalopram (20-60 mg), escitalopram (10-30 mg), fluvoxamine (up to 200 mg), fluoxetine (40-80 mg), and sertraline (100-200 mg) are associated with improvement in BED-related symptoms.[111,114,115,117] This includes a reduction in binge frequency, improved mood symptoms, and reduced obsessive-compulsive symptoms, though not all studies have included each of these outcome measures in their methodology.[117] The majority of the data are with antidepressant doses, and interestingly, the combination of antidepressants with CBT has not borne out improved outcomes in most studies.[105,107-109] Vortioxetine, with a target dose of 20 mg daily, failed to separate from placebo in a recent clinical trial, although a naturalistic study (mean dose 15.8 mg daily) showed improvement in BED symptoms in participants with comorbid MDD.[118,119]

Atomoxetine (40-120 mg) and venlafaxine (75-300 mg) have evidence to support improvement in BED symptoms with reduction in binge frequency, reduced BMI, weight loss, and improved mood symptoms.[117] Duloxetine has also been studied in comorbid depression with reductions in binge-eating and depressive symptoms.[120] Although bupropion has not shown improvement in BED outcomes with the exception of two case reports, naltrexone/bupropion had resulted in Binge Eating Scale score improvement and depressive symptoms with further research warranted.[121,122]

Lisdexamfetamine is a prodrug of dextroamphetamine and is FDA approved for the treatment of moderate to severe BED (30 mg initially and titrated to 50-70 mg daily). Clinical trials demonstrated reductions in numbers of binge days per week, a greater percentage of patients with global clinical improvement, a higher percentage achieving a 4-week cessation of binge episodes, functional outcomes, and improvement in obsessive-compulsive psychometric measures.[123,124] The aforementioned outcomes are supported out to 52 weeks.[125-127] An additional stimulant, methylphenidate (18-72 mg daily), has been compared to CBT with similar remission rates.[122]

Topiramate (25-300 mg daily) reduced binge frequency, body weight, and BMI, and remission rates were higher when combined with CBT.[128] Combination of phentermine/topiramate was effective for weight loss and improvement in binge-episode frequency and psychopathology in two open-label studies and a small clinical trial.[129] Zonisamide (100-600 mg/day) alone and in combination with CBT over the course of 16-week and 1-year studies demonstrated efficacy at reducing binge-eating and weight loss; however, there were high dropout rates due to intolerability.[94]

Orlistat (120 mg given three times daily), along with calorie-restricted diet, produced weight reduction in obese patients with BED.[130] Other medications used to treat obesity are being explored as possible treatment options. Liraglutide specifically has demonstrated improvement in binge eating, but this patient population was not formally diagnosed with BED.[78]

Current literature suggests that lisdexamfetamine, SSRIs, topiramate, and dasotraline (dopamine/norepinephrine reuptake inhibitor) hold the most promise in the short term, but long-term data is lacking.

Combination Therapy

The combination of pharmacologic and nonpharmacologic measures for BED has been examined in 12 randomized clinical trials with no identified benefit. Two randomized clinical trials have added antiseizure medications to CBT (zonisamide and topiramate) with significantly greater reductions in select binge-eating outcomes and BMI than CBT alone.[104]

EVALUATION OF THERAPEUTIC OUTCOMES

Eating Disorder Guideline Summary

Formalized treatment guidelines are available to assist in the management of eating disorders, specifically for AN, BN, and BED.[30,35,60,117,131] Although guidelines are an important tool to aid in the decision-making process in developing treatment and management strategies, it is important to note variation in release dates of the various guidelines as this affects the information able to be included at the time of publication.

Anorexia Nervosa

A combination of subjective and objective measures is used to assess response in patients with AN. A reduction in the frequency and severity of abnormal eating habits, normalized exercise patterns and laboratory tests, and a sustained weight close to age-matched non-affected individuals are key indicators of response. A diary recording exercise frequency, menses, food intake, patterns of eating, and associated feelings while eating is a useful tool to track progress, especially in the outpatient setting. Weekly weigh-ins on the same scale, preferably at a clinician's office, help monitor progress early in treatment and reduce the focus on weight and anxiety caused by the variability found among different scales. Follow-up laboratory tests and ECGs are not part of routine monitoring unless the patient is restricting food intake, is purging, or continues to lose weight despite treatment. Inpatients require daily assessment of weight and caloric intake, vital signs, and urine output because of the severity of their illness. This may include monitoring of bathroom privileges early in their care. A healthy weight gain of not more than 0.2 to 0.5 kg (0.4-1.1 lb) per week, toward a goal of 90% to 95% of normal weight or a BMI greater than 18.5 kg/m^2 is a critical sign of treatment success. A patient's use of coping skills and contingencies for dealing with stress, other than manipulating food consumption, also should be assessed. Antidepressants can assist in alleviation of persistent depression, anxiety, and obsessions, after weight restoration. Improvement in mood is expected to occur within 8 weeks. Patients receiving TCAs should be evaluated for dry mouth, constipation, hypotension, and sedation and patients receiving SSRIs should be monitored for agitation, medication-induced anorexia, nausea, weight loss, and insomnia. The decision to use long-term medication must be based on specific and sustained improvement in the target symptoms, balanced against adverse effects.

Recent research has focused on quality of life as a primary outcome measure compared to targeting specific symptoms of AN as quality of life is generally lower in individuals with a history or clinical presence of an eating disorder. Preliminary findings, however, suggest that improvement in quality of life is in part dependent on symptom improvement and weight gain, thus weight gain and behavioral change should remain the focus of treatment.

Bulimia Nervosa

Individualized treatment and monitoring plans begin with a thorough assessment describing the baseline frequency and severity of treatment-responsive target symptoms and other associated findings. This must be comprehensive, as a patient can hide their illness by shifting from one type of behavior to another (eg, exercise to purging).

This comprehensive assessment should include a description of psychiatric symptoms, physical findings, frequency and severity of binge–purge episodes, laxative and ipecac use, exercise patterns, and laboratory and ECG abnormalities. Interpersonal and relationship problems should also be evaluated. Some findings indicating a more chronic course of illness, such as salivary gland inflammation and erosion of dental enamel, can take months to reverse or might never normalize, making them poor indicators of early treatment response. Data describing a patient's baseline level of functioning and previous response to treatment should be used to set goals in the current treatment plan.

Antidepressant response usually occurs within 4 to 8 weeks after treatment onset. If response does not occur, binge–purge behavior should be considered as a factor potentially contributing to medication malabsorption. If this behavior is not present, then every attempt should be made to maximize the dose. TCA serum concentration monitoring should be done periodically (eg, every 3 to 6 months if a patient is responding and tolerating the medication, or more frequently if clinically indicated). Evaluation of adverse medication effects should be part of the monitoring plan. If the patient responds, they should be followed for 6 to 12 months, and then reassessed for the need for ongoing medication. If they relapse after medication discontinuation, then pharmacotherapy should be restarted. There is an increased risk of suicidality associated with antidepressant use in major depression; thus suicidality should be assessed following antidepressant initiation, especially early in therapy. Chapter 88 includes further details and more comprehensive information related to antidepressant use.

Patients receiving eating disorder treatment on an outpatient basis present a particular challenge to clinicians, as impulsivity associated with BN can increase the risk for suicide. To reduce the risk of medication overdoses, prescriptions should be limited to small supplies. In addition, clinicians should be alert to persons who make large or frequent purchases of laxatives or ipecac syrup, as this is an indicator of possible purging behaviors.

Binge-Eating Disorder

Similar to BN, the frequency and severity of binge episodes should be monitored. In addition, psychiatric symptoms, physical findings, and interpersonal problems should be assessed. Patients with BED are at a higher risk of suicide (suicide attempt prevalence 22.9%) and thus close monitoring of mood should be included in the treatment plan.[132,133]

Evaluation of adverse effects should be monitored as indicated during discussion of AN and BN. If weight loss is being pursued, all appropriate measures such as weight, calculated BMI, and waist circumference are indicated. Please refer to Chapter 167, for further details and more comprehensive information related to treatment of obesity. Metabolic parameters should be periodically assessed and monitored. There is a relative paucity of literature to guide length of treatment, although recommendations for BN could be extrapolated to BED.

CONCLUSION

The treatment of AN is complex and involves preferred strategies of psychotherapy that may include CBT, DBT, and nutritional counseling among several others. Pharmacologic strategies are not aimed at core AN symptom reduction, but rather concurrent mental illness that often accompanies AN. This can include the use of both antidepressants and antipsychotics. Antidepressants have not been shown to be clinically meaningful for core AN symptoms, but may be appropriate with co-occurring depression. Antipsychotics have also been shown to aide in managing anxiety, paranoia, and obsessions associated with weight gain, while also helping to improve patient BMIs.

Assessment of BN patients include frequency and severity of binge–purge episodes, laxative and ipecac use, exercise patterns, physical and laboratory findings, and other psychiatric symptoms. Cognitive behavioral therapy is the nonpharmacologic treatment of choice. Antidepressants, particularly SSRIs, are used in the acute and maintenance phases of BN adjunctively with nonpharmacologic approaches. Antidepressant response usually occurs in 6 to 8 weeks. Monitoring for response as well as adverse effects is a critical part of the plan.

The treatment of BED necessitates a holistic approach including nonpharmacologic therapy such as CBT along with nutritional guidance and weight loss, if applicable. Lisdexamfetamine is the sole FDA-approved agent for treatment of moderate to severe BED, although evidence exists for antidepressants and antiseizure medications, namely topiramate. As with all eating disorders, monitoring for adverse effects and ongoing BED symptoms should be assessed regularly.

ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
5-HTTLPR, SLC6A4	serotonin transporter
AN	anorexia nervosa
BDNF	brain-derived neurotrophic factor
BED	binge-eating disorder
BMI	body mass index
BN	bulimia nervosa

CBT	cognitive behavioral therapy
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computerized tomography
DBT	dialectical behavior therapy
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition
ECG	electrocardiogram
EEG	electroencephalogram
ESRI	estrogen receptor I gene
GI	gastrointestinal
IPT	interpersonal therapy
MAOI	monoamine oxidase inhibitor
MRI	magnetic resonance imaging
NES	night eating syndrome
OCD	obsessive-compulsive disorder
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

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SELF-ASSESSMENT QUESTIONS

1. Suspected deficiencies of serotonin have commonly been linked to anorexia nervosa, primarily thought to be the result of a reduction in the intake of which of the following amino acids?

   A. Glycine

   B. Tyrosine

   C. Glutamine

   D. Tryptophan

2. Which of the following is/are required when considering a diagnosis of anorexia nervosa?

   A. Restriction of energy intake leading to low body weight

   B. Undue influence of body shape on self-evaluation

   C. Behavior that interferes with weight gain

   D. All of the above

3. A 16-year-old female is being evaluated for a possible diagnosis of anorexia nervosa. Their history reveals that they have a sister diagnosed with anorexia nervosa, their father is diagnosed and treated for bipolar disorder, Type 1, and they have been treated for asthma since a young age. They have also been regularly using cannabis and alcohol since the age of 13. Which of the following are considered positive risk factors for developing anorexia nervosa?

   A. Substance use disorder

   B. Sibling with anorexia nervosa

   C. Presence of a mood disorder

D. All of the above

4. A 17-year-old with anorexia nervosa is currently undergoing caloric restoration at a rate 800 cal/day (3,300 J/day). The physician is most worried about:

   A. Refeeding syndrome

   B. Cardiac arrhythmia

   C. Unfeeding syndrome

   D. Renal failure

5. The second-generation antipsychotic olanzapine has demonstrated effectiveness in combination with day hospital treatment at increasing weight gain and also as treatment alone to improve BMI. The results of a recent meta-analysis examining the impact of olanzapine, quetiapine, and risperidone discovered which of the following?

   A. Olanazpine and quetiapine produced significant BMI gains

   B. Risperidone produced significant BMI gains, but had higher rates of EPS

   C. Olanzapine, quetiapine, and risperidone increased weight gain and BMI

   D. Olanzapine, quetiapine, and risperidone did not significantly impact BMI

6. Which of the following lacks maladaptive compensatory mechanisms such as over-exercise or purging?

   A. Anorexia nervosa

   B. Bulimia nervosa

   C. Binge-eating disorder

   D. None of the above

7. Which of the following pairs share the core feature of binge-eating?

   A. Binge-eating disorder and anorexia nervosa

   B. Binge-eating disorder and bulimia nervosa

   C. Anorexia nervosa and bulimia nervosa

   D. Anorexia nervosa and night eating syndrome

8. In patients with binge-eating disorder, which of the following conditions are they at an increased risk of developing?

   A. Refeeding syndrome

   B. Diabetes mellitus type 2

   C. Osteopenia

   D. Dental caries

9. A 23-year-old patient presents to your outpatient clinic. They report a recent diagnosis of binge-eating disorder and is interested in what types of therapy might be most helpful. They denies any previous therapy. What would you recommend?

A. Cognitive behavioral therapy (CBT)

B. DBT (dialectic behavioral therapy)

C. Mindfulness

D. Behavioral weight loss (BWL)

10. A 30-year-old patient is picking up their prescriptions at your community pharmacy. Upon review, the patient confirms that they are picking up their monthly oral contraceptives, duloxetine capsules 60 mg by mouth once daily, sumatriptan tablets 100 mg as needed for migraines, and tramadol tablets 50 mg every 6 hours as needed for pain. They reports they would like to start a medication for their "secret binges," which their physician has diagnosed as binge-eating disorder. Which of the following options would you recommend?

A. Lisdexamfetamine

B. Sertraline

C. Bupropion

D. Topiramate

11. Nonpharmacologic strategies in the treatment of BN are critical to success. Which nondrug strategy offers the most robust evidence supporting its benefit?

A. Sixteen to 20 sessions of cognitive behavioral therapy over 4 to 5 months

B. Family-based therapy

C. Interpersonal psychotherapy

D. Motivational teaching and self-help guides

12. JS is a 22-year-old female diagnosed with bulimia nervosa. Which characteristic below does not fit with the diagnostic criteria for BN?

A. Average height and weight at presentation but has periods where she fluctuates between overweight and underweight

B. Presenting symptoms of anxiety, history of substance use, and difficulty with personal relationships

C. Several times a month she eats excessively and feels very guilty about it afterward

D. Lack of concern over her body image

13. All of the following are acceptable pharmacologic treatments for bulimia nervosa, except:

A. Fluoxetine 60 mg/day

B. Phenelzine 90 mg/day

C. Bupropion 300 mg/day

D. Desipramine 150 mg/day

14. CB is a 24-year-old who presents with a 3-month history of symptoms including depressed mood, poor sleep, and weight loss due to lack of appetite and fear that their food may be tainted with poison. What characteristics should be present to support a differential diagnosis of eating disorder?

A. Disturbed body image

B. Overriding drive for thinness

C. Increased energy directed at losing weight

D. All of the above

15. Patients diagnosed with BN lack control over their eating and participate in recurrent compensatory behavior to prevent weight gain. The non-purging subtype engages in behaviors including all of the following, except:

A. Self-induced vomiting

B. Overuse of laxatives, diuretics, or enemas

C. Strict dieting or fasting

D. Excessive exercise

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Serotonin, norepinephrine, and dopamine have been studied extensively with well-described roles in controlling eating behaviors. Special emphasis has been placed on the role of serotonin (5-HT), specifically noting reduced cerebrospinal fluid (CSF) basal concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of 5-HT, as well as increased binding of 5-HT1A receptors and reduced binding of 5-HT2A receptors in different regions within the central nervous system (CNS). Reduced dietary intake of tryptophan-containing leads to reduced levels of tryptophan, a requirement for the development of 5-HT (see "Pathophysiology" section).

2. **D.** The presentation of AN includes a recent period of weight loss as well as associated behaviors to promote this such as vomiting, limiting food intake, and excessive exercise. Current diagnostic criteria for AN include the restriction of energy intake relative to requirements that leads to low body weight contextually as it relates to age, sex, developmental trajectory, and physical health. The *DSM-5* further classifies AN as restricting type in which patients restrict food intake with no binge-eating or purging behavior over the past 3 months, or binge-eating/purging type, in which patients regularly participate in bingeing or purging over the prior 3 months. The severity of AN is based upon body mass index (BMI) in adults and BMI percentiles in children and adolescents. Comorbid psychiatric conditions, such as major depression, are frequent but should initially be considered secondary to starvation and not a true mood disorder (see "Clinical Presentation" section).

3. **D.** Specific risk factors for AN include being female, having a sibling with AN, the presence of mood disorders in family members, and comorbid anxiety, personality, or substance use disorders (see "Clinical Presentation" section).

4. **C.** Current clinical evidence suggests a controlled weight gain of 0.9 to 1.4 kg (2-3 lb) per week in inpatient settings and 0.2 to 0.5 kg (0.5-1.1 lb) per week in outpatient settings. Refeeding recommendations vary between younger patients and adults and are considered controversial. An acceptable approach for younger patients is to begin refeeding at 800 to 1,000 cal/day (3,300-4,200 J/day), while others suggest a more aggressive approach.[71] Adults may be considered for refeeding initiation in the range of 1,000 to 1,600 cal/day (4200-6700 J/day) (30-40 cal/kg/day [130-170 J/kg/day]) with slow titration (every other day) upward (100-200 cal/day [420-840 J/day]) until they begin to demonstrate sustained weight gain or achieve target weights. This can require the intake of an additional 3,500 to 7,000 cal (14,600-29,300 J) per week. Slow refeeding has long been considered important to prevent psychological and medical consequences, including the severe electrolyte disturbance that results from insulin surges known as refeeding syndrome, which can result in death. A criticism is that too conservative of an approach results in further weight loss early in treatment (unfeeding syndrome), contributing to a failure to achieve nutritional recovery goals (See "Treatment" section).

5. **D.** Olanzapine in combination with day hospital treatment has been shown to be more effective than day hospital treatment alone in achieving greater weight gain and reducing obsessive symptoms. In addition, an outpatient study examining olanzapine versus placebo, independent of concurrent psychotherapy, demonstrated significant improvement in BMI. Despite these reported benefits, a meta-analytic review of second-generation antipsychotics that included olanzapine, quetiapine, and risperidone did not find significant differences in BMI gains or eating disorder psychometric outcome assessments (see "Treatment" section).

6. **C.** The symptoms of AN can include purging, restricting caloric intake, and overexercise. BN includes purging behaviors. Binge-eating disorder

(BED) results in no maladaptive behaviors (see "Clinical Presentation" section).

7. **B.** Binge-eating is not a core feature of AN but is a subtype. Night-eating syndrome can result in excessive food consumption, although since that option is paired with AN, it is not the correct choice. BED and BN share binge-eating as a core diagnostic criterion (see "Clinical Presentation" section).

8. **B.** Refeeding syndrome is associated with caloric restoration in anorexia nervosa. Osteopenia is a potential long-term complication of suppressed estrogen associated with starvation seen in anorexia nervosa. Dental caries can be seen in patients with frequent purging. As patients with binge-eating disorder may be overweight or obese, this increases the risk of diabetes mellitus type 2 (see "Medical Complications of Eating Disorders" section).

9. **A.** For the treatment of binge-eating disorder, DBT, BWL, and mindfulness are not considered first-line (see Fig. e83-2).

10. **D.** The patient is currently on three serotonergic medications: duloxetine, sumatriptan, and tramadol (although it is now generally accepted that triptans do not increase the risk of serotonin syndrome). Lisdexamfetamine may also increase the already elevated risk of serotonin syndrome. In addition, there is a drug-drug interaction between lisdexamfetamine and duloxetine mediated through CYP2D6. Sertraline is a selective serotonin reuptake inhibitor which would also increase risk of serotonin syndrome. Evidence for bupropion in binge-eating disorder is limited to case reports. Topiramate has evidence to support a reduction in binge frequency and body weight with increased remission rates. The patient should be educated on the risk of fetal harm with use of topiramate if they become pregnant (see Fig. e83-2).

11. **A.** Only CBT has the strongest evidence supporting its benefit in managing BN. Current treatment guidelines suggest that CBT should consist of 16 to 20 sessions over a 4- to 5-month period. Thirty percent to 50% of individuals who receive CBT for BN may be abstinent from binge-eating and purging behaviors by conclusion of the treatment. Interpersonal psychotherapy also plays a role and has a moderate degree of evidence to support its use, but it is considered less effective than CBT. Psychodynamic therapy as well as family-based therapy is also viable options for treatment of adolescents with BN. Programs using motivational teaching and self-help guides based on CBT have shown promise (see Fig. e83-2).

12. **D.** The general clinical presentation of BN includes presence of binge episodes that only stop when abdominal pain emerges, purging occurs, or the episode is interrupted by another person; a pattern of severe dieting following by further binge-eating; and concern about body image, although this does not have the excessive drive for thinness characteristic of AN (see "Clinical Presentation" section).

13. **C.** Selective serotonin reuptake inhibitors are the preferred agents because of their tolerability and because they have been studied in the largest number of patients. Fluoxetine remains the only medication with FDA approval for BN. Efficacy of other SSRI agents is still lacking, but an alternative SSRI may be considered in clinical practice for patients who do not respond to fluoxetine.[94] Tolerability is the primary criterion for selecting an antidepressant in the treatment of BN because of patients' heightened sensitivity to adverse effects and the lack of a clear difference in efficacy between the classes. Even though there is a suggestion that MAOIs produce the most robust effect, the risk of using these medications in impulsive patients limits their use.[63] Selective norepinephrine reuptake inhibitors have shown promising results; however, the data supporting their use are limited to case reports. Bupropion, a norepinephrine–dopamine reuptake inhibitor, is contraindicated in patients diagnosed with BN because of the increased risk of seizures seen in patients with an eating disorder (see "Treatment" section).

14. **D.** Eating abnormalities can be a component of or share similar symptoms with psychiatric disorders including depression, obsessive-compulsive disorder, and schizophrenia, thus they should be part of the differential diagnoses of eating disorders. The salient differences are the overriding drive for thinness, disturbed body image, increased energy directed at losing weight, and binge-eating episodes that are relatively specific for eating disorders (see "Clinical Presentation" section).

15. **A.** To meet the *DSM-5* criteria, the binges and compensatory behaviors must occur on average at least once weekly for 3 months. Bulimia nervosa can further be differentiated by purging type (regularly engages in self-induced vomiting or the misuse of laxatives, diuretics, or enemas) or non-purging type (uses other inappropriate compensatory behaviors, such as fasting or excessive exercise, but does not engage in purging activities) (see "Clinical Presentation" section).