Dear Healthcare Professional,

Welcome to the Cleveland Clinic Physician’s Guide to Obesity, an information-packed tool brought to you by the Cleveland Clinic’s Disease Management Project (DMP) in collaboration with BulletinHealthcare, the leading provider of medical news updates to healthcare professionals like yourself.

This guide covers a wide range of topics, from signs and symptoms and comorbidities to treatment options including lifestyle modification, medications, surgery, and more. And it was researched and written by leading experts in the field—Dr. Stacy Brethauer, Dr. Sangeeta Kashyap, and Dr. Philip Schauer.

We hope you find the Cleveland Clinic Physician’s Guide to Obesity to be helpful, informative, and of value in your efforts to diagnose, treat, and provide positive patient outcomes. We look forward to hearing your thoughts about this content. Please send me your comments at diseasemanagement@ccf.org.

William Carey, MD
Editor-in-Chief
Disease Management Project
Cleveland Clinic

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The information in this educational activity is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient’s medical condition. The viewpoints expressed in this educational activity are those of the authors/faculty. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through this educational activity.
Introduction

Definition and Etiology

Obesity has become an important public-health problem in industrialized countries throughout the world. The body mass index (BMI = weight (in kg/height² (in m²)) is the primary measurement used to categorize obese patients (Table 1). Excess body weight (EBW) is defined as the amount of weight that is in excess of the ideal body weight (IBW). Ideal body weight is conventionally determined by the Metropolitan Life Tables, or as a BMI of 25 kg/m². In 1991, the National Institutes of Health defined morbid obesity as a BMI of ≥ 35 kg/m² and severe, obesity-related comorbidity as a BMI of ≥ 40 kg/m².

Table 1 Definitions of Obesity

<table>
<thead>
<tr>
<th>Category</th>
<th>Body Mass Index (kg/m²)</th>
<th>Over Ideal Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td></td>
</tr>
<tr>
<td>Obesity (class 1)</td>
<td>30-34.9</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>Severe obesity (class 2)</td>
<td>35-39.9</td>
<td>&gt;100%</td>
</tr>
<tr>
<td>Severe obesity (class 3)</td>
<td>40-49.9</td>
<td></td>
</tr>
<tr>
<td>Superobesity</td>
<td>&gt;50</td>
<td>&gt;250%</td>
</tr>
</tbody>
</table>

The development of obesity involves the interactions between excessive caloric intake, inefficient use of food energy, reduced metabolic activity, a reduction in the thermogenic response to meals, and an abnormally high set point for body weight. Genetic, environmental, and psychosocial factors all contribute to this problem.

Prevalence and Risk Factors

The prevalence of obesity in the United States has increased from 15% in 1980 to 36% in 2010. The prevalence of extreme obesity (BMI ≥ 40 kg/m2) is 4.4% in men and 8.2% in women. The prevalence of childhood and adolescent obesity has tripled since 1980 and, currently, 17% of U.S. children and adolescents are obese. Obesity and morbid obesity affect women and minorities (particularly middle-aged black and Hispanic women) more than white males. However, in almost every age and ethnic group, the prevalence of overweight or obesity exceeds 50%.

Recent studies also have delineated the influence of childhood weight on adulthood weight. Being overweight during older childhood is highly predictive of adult obesity, especially if a parent also is obese. Being overweight during the adolescent years is an even greater predictor of adult obesity. Obesity is now the second-leading cause of preventable death in the U.S. after cigarette smoking, despite expenditures of over $45 billion annually on weight-loss products.
Pathophysiology and Natural History

Adipose tissue is primarily stored subcutaneously and in the abdominal cavity. In general, females are more likely to deposit fat in the peripheral tissues; males tend to deposit it in the abdominal compartment. As obesity develops, the size and number of fat cells increase. As fat cells grow, they release increasing amounts of cytokines and lower amounts of adiponectin. These changes have deleterious effects on glucose and lipid metabolism, and contribute to the proinflammatory state associated with obesity.

Obesity shortens the life span of those who suffer with it. The mortality rate of an individual with a BMI \( \geq 40 \text{ kg/m}^2 \) is double that of a normal-weight individual.\(^5\) It is estimated that a man in his 20s with a BMI \( \geq 45 \text{ kg/m}^2 \) has a 22% reduction in life expectancy, a decrease of 13 years.\(^6\) Most obesity-related deaths result from complications related to diabetes, cancer, and cardiovascular disease. Worldwide, approximately 2.5 million deaths occur annually because of obesity-related comorbidities.

Signs, Symptoms, and Related Diseases

There are more than 30 comorbid conditions associated with severe obesity. Insulin resistance and diabetes mellitus occur in 15% to 25% of obese patients. Increased abdominal fat in obese patients raises the intra-abdominal pressure and contributes to gastroesophageal reflux, stress urinary incontinence, venous stasis disease, and abdominal hernia. Fatty deposits in the liver can progress to nonalcoholic steatohepatitis (NASH) and, ultimately, to liver failure. Excess weight causes joint and back stress that can lead to debilitating joint disease.

The low-grade inflammatory state associated with morbid obesity has been implicated in the development of vascular and coronary artery disease, and the hypercoagulable state seen in these patients. Obese patients have impaired pulmonary function, particularly decreased functional residual capacity, and frequently suffer from asthma, obstructive sleep apnea, and obesity hypoventilation syndrome (also known as Pickwickian syndrome and encompassing chronic hypoxemia, hypercarbia, pulmonary hypertension, and polycythemia). Other comorbidities include hypertension, dyslipidemia, asthma, and sex-hormone dysfunction. Obesity is associated with an increased incidence of cancer of the uterus, breast, ovaries, prostate, and colon; skin infections; urinary-tract infections; migraine headaches; depression; and pseudotumor cerebri.

Diagnosis and Evaluation of Comorbidities

The diagnosis of morbid obesity is established by determining the patient's BMI and the presence of any significant comorbid conditions. A thorough history, physical examination, and focused testing will uncover previously undiagnosed comorbidities in up to two-thirds of obese patients.

Visceral, or central, fat is more metabolically active than peripheral fat and is associated with type 2 diabetes, dyslipidemia (elevated triglyceride and reduced high-density lipoprotein [HDL] levels), high blood pressure, and increased risk for cardiovascular atherosclerotic disease. The waist-to-hip ratio helps to identify patients with excess visceral adiposity. Women with a waist-to-hip ratio >0.8 and men with a ratio >1.0 are considered to have excess central adiposity that confers risk for developing the metabolic syndrome. The diagnostic criteria for the metabolic syndrome are shown in Table 2.
### Table 2 Adult Treatment Panel III Criteria for the Metabolic Syndrome*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central obesity</strong></td>
<td></td>
</tr>
<tr>
<td>Waist circumference in men</td>
<td>&gt;102 cm</td>
</tr>
<tr>
<td>Waist circumference in women</td>
<td>&gt;88 cm</td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td><strong>Low high-density lipoprotein cholesterol</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td><strong>High blood pressure</strong></td>
<td>≥130/≥85 mmHg</td>
</tr>
<tr>
<td><strong>Fasting blood glucose</strong></td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

*Three or more of these criteria need to be present.


The pretreatment evaluation performed at the Cleveland Clinic is consistent with published guidelines.7 Because obese persons are at greater risk for cardiovascular disease, a baseline electrocardiogram (ECG) should be performed. Cardiology evaluation is carried out when there is evidence of cardiac disease based on clinical symptoms or ECG findings. Chest radiography and baseline laboratory testing, including a complete blood count, chemistry panel, liver-function tests, thyroid-function tests, and a lipid profile, should be obtained as well.

Obstructive sleep apnea frequently goes unrecognized in this patient population until a thorough history prompts further evaluation. Patients with symptoms of loud snoring, daytime hypersomnolence, or a neck circumference ≥ 43 cm should undergo polysomnography and, if positive, be treated with continuous positive airway pressure (CPAP). Asthma and obesity hypoventilation syndrome also are severe pulmonary complications of obesity and should be evaluated by a pulmonologist. Dietary counseling and psychological testing are required for patients who are referred for bariatric surgery.

### Treatment

#### Lifestyle Modifications

According to the clinical guidelines published by the American College of Physicians, all patients with a BMI ≥ 30 kg/m² should be counseled intensively on lifestyle and behavior modifications, such as appropriate diet and exercise.8,9 An algorithm published by the American College of Physicians for medical management of an obese patient is shown in Figure 1.9 The patient's goals for weight loss should be individually determined and may encompass other related parameters, such as decreasing blood pressure or fasting blood glucose levels. When establishing realistic weight-loss goals, it is important to realize that modest weight loss (10%-15%) is sufficient to result in health benefits.10,11
Figure 1 Algorithm for the Medical Management of Obesity

General dietary guidelines for achieving and maintaining a healthy weight include direction to eat a variety of nutritious foods in order to avoid vitamin deficiencies. The patient should be advised to avoid foods that are high in fat and simple sugars, and to increase dietary fiber intake. Meal-replacement shakes and behavior-modification strategies can increase adherence. The patient should be directed to maintain a diet in which 50% to 55% of calories come from complex carbohydrates. In addition, it is helpful to educate the patient about appropriate portion sizes and the caloric content of foods, as recommended by several national scientific organizations, such as the American Dietetic Association and American Diabetes Association. Referral to a registered dietitian can help the patient initiate and adhere to these dietary guidelines.

Every physician should include a graded exercise regimen as part of a comprehensive lifestyle-modification plan. Moderate exercise has been shown to decrease blood pressure; increase HDL levels and reduce triglyceride levels; and is predictive of maintenance of weight loss and delaying onset of type 2 diabetes. General exercise recommendations include 20 to 30 minutes of moderate exercise 5 to 7 days a week, up to 60 minutes per day most days of the week for maintenance of weight, and 90 minutes a day for achieving weight loss.
**Medical Options**

Pharmacologic therapy can be considered in an obese patient who has significant comorbidities or has failed to achieve weight-loss goals through lifestyle modification alone. Before initiating therapy, however, the clinician must inform the patient of any side effects associated with the drug, the lack of long-term safety data, and the temporary nature of the weight loss achieved through the use of medications. Table 3 lists the medications reviewed in the 2013 American College of Physicians clinical practice guideline for obesity management. Cardiovascular side effects were noted with the appetite suppressant sibutramine, resulting in its removal from the market.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine/Topiramate</td>
<td>Appetite suppressant</td>
<td>Dizziness, dry mouth, constipation</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Appetite suppressant</td>
<td>Nausea, dizziness</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Appetite suppressant: sympathomimetic amine</td>
<td>Cardiovascular, gastrointestinal</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Appetite suppressant: sympathomimetic amine</td>
<td>Palpitations, tachycardia, insomnia, gastrointestinal</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Lipase inhibitor: decreased absorption of fat</td>
<td>Diarrhea, flatulence, bloating, abdominal pain, dyspepsia</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Appetite suppressant: mechanism unknown</td>
<td>Paresthesia, insomnia, central nervous system effects</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Appetite suppressant: selective serotonin reuptake inhibitor</td>
<td>Agitation, nervousness, gastrointestinal</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Appetite suppressant: selective serotonin reuptake inhibitor</td>
<td>Agitation, nervousness, gastrointestinal</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Mechanism unknown</td>
<td>Paresthesia, changes in taste</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Mechanism unknown</td>
<td>Somnolence, dizziness, nausea</td>
</tr>
</tbody>
</table>

The choice of agent depends on the side-effect profile and the patient’s ability to tolerate those side effects. The amount of weight loss achieved through pharmacologic therapy is generally modest (< 5 kg at 1 year). However, even modest weight loss can slow the progression of diabetes and reduce cardiovascular risk factors. However, there is no evidence that modest weight loss reduces mortality rates in these patients.

The optimal duration of treatment with obesity medications has not yet been determined. Data from randomized controlled trials are only available for up to 12 months of therapy. There are no long-term data on whether these drugs decrease morbidity or mortality from obesity-related conditions.
Indication
BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:
- 30 kg/m² or greater (obese), or
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes).

Limitations of Use
- The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss, including prescription drugs (eg, phentermine), over-the-counter drugs, and herbal preparations, have not been established.
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

Important Safety Information
Contraindication
- BELVIQ should not be taken during pregnancy or by women who are planning to become pregnant.

Warnings and Precautions
- BELVIQ is a serotonergic drug. The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors, serotonergic drugs, and dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists,
particularly when used in combination. Patients should be monitored for the emergence of serotonin syndrome symptoms or NMS-like reactions, including agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, diarrhea, and muscle rigidity. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

- Patients should not take BELVIQ in combination with drugs that have been associated with valvular heart disease (e.g., cabergoline). In clinical trials, 2.4% of patients taking BELVIQ and 2.0% of patients taking placebo developed valvular regurgitation: none of these patients were symptomatic. BELVIQ should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of BELVIQ should be considered.

- Impairment in attention, memory, somnolence, confusion, and fatigue, have been reported in patients taking BELVIQ. Patients should not drive a car or operate heavy machinery until they know how BELVIQ affects them.

- The recommended dose of 10 mg twice daily should not be exceeded, as higher doses may cause euphoria, hallucination, and dissociation. Monitor patients for the development or worsening of depression, suicidal thoughts or behaviors, and/or any changes in mood. Discontinue BELVIQ in patients who develop suicidal thoughts or behaviors.

- Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus who are being treated with antidiabetic medications, so measurement of blood sugar levels before and during treatment with BELVIQ is recommended. Decreases in doses of antidiabetic medications or changes in medication regimen should be considered.

- Men who experience priapism should immediately discontinue BELVIQ and seek emergency medical attention. BELVIQ should be used with caution with erectile dysfunction medications. BELVIQ should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease).

- Because BELVIQ may cause a slow heartbeat, it should be used with caution in patients with a history of bradycardia or heart block greater than first degree.

- Consider monitoring for CBC changes, prolactin excess, and pulmonary hypertension.

**Most Common Adverse Reactions**

- In patients without diabetes: headache (17%), dizziness (9%), fatigue (7%), nausea (8%), dry mouth (5%), and constipation (6%).

- In patients with diabetes: hypoglycemia (29%), headache (15%), back pain (12%), cough (8%), and fatigue (7%).

**Nursing Mothers**

- BELVIQ should not be taken by women who are nursing.

BELVIQ is a federally controlled substance (CIV) because it may be abused or lead to dependence.

*Please see Brief Summary of Prescribing Information and references on adjacent pages.*


BRIEF SUMMARY: For prescribing information, see package insert.

INDICATIONS AND USAGE
BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

• 27 kg/m² or greater (overweight), or
• 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

Limitations of Use
• The safety and efficacy of combination of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal products has not been established.

• The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

DOSAGE AND ADMINISTRATION
The recommended dose of BELVIQ is 10 mg administered orally daily. Do not exceed recommended dose. BELVIQ can be taken with or without food. Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, discontinue BELVIQ, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

CONTRAINDICATIONS
WARNINGs AND PRECAUTIONS
Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions. BELVIQ is a serotonin antagonist. The combination of BELVIQ with other serotonergic agents, including antidepressants (e.g., fluoxetine, amitriptyline, desipramine, or tramadol), SSRIs, 5-HT₂A receptor agonists (e.g., ergotamine, dihydroergotamine), MAO inhibitors, or selective serotonin reuptake inhibitors (SNRIs) may result in a serotonin syndrome. This syndrome may be manifested by the following: mental status changes (e.g., agitation, hallucinosis, coma), autonomic instability (e.g., tachycardia, hyperpyrexia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, hyperpyrexia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability (with possible rapid fluctuations in vital signs), and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

Valvular Heart Disease. Regurgitant cardiac valve disease, primarily affecting the mitral and/or aortic valves, has been reported in patients who took serotonin drugs with 5-HT₂A receptor activity. The mechanism of the regurgitant valve disease is thought to be activation of 5-HT₂A receptors on cardiac interstitial cells. At therapeutically effective levels, BELVIQ is selective for 5-HT₂A receptors as compared to 5-HT₁A receptors. In clinical trials of 1-year duration, 2.4% of patients treated with BELVIQ and 2.0% of patients treated with placebo developed electrocardiographic criteria for valvular regurgitation at one year (mild or moderate aortic regurgitation and/or moderate or greater mitral regurgitation). None of these patients were symptomatic.

BELVIQ has not been studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease. Preliminary data suggest that 5-HT₁A receptors may be overexpressed in congestive heart failure. Therefore, BELVIQ be used with caution in patients with congestive heart failure.

BELVIQ is not recommended in combination with serotonergic and dopaminergic drugs that are potent 5-HT₂A receptor agonists and are known to increase the risk for cardiac valvulopathy (e.g., cabergoline). Patients who develop signs or symptoms of valvular heart disease, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur while being treated with BELVIQ should be evaluated and discontinuation of BELVIQ should be considered. Concomitant clinical trials of at least one year in duration, impairments in attention and memory were reported in patients treated with BELVIQ. A total of 1969 patients were exposed to BELVIQ 10 mg twice daily for 1 year and 426 patients were exposed for 2 years.

In clinical trials of at least one year in duration, 8.6% of patients treated with BELVIQ developed hypertension (with or without antihypertensive treatment due to adverse events). In this population, the addition of an antihypertensive was required in 6.7% of placebo-treated patients.

Most Common Adverse Reactions

- Nausea 264 (8.3) 170 (5.3)
- Diarrhea 207 (6.5) 179 (5.6)
- Constipation 186 (5.8) 125 (3.9)
- Dry mouth 169 (5.3) 74 (2.3)
- Vomiting 122 (3.8) 63 (2.1)

- Fatigue 229 (7.2) 114 (3.8)
- Infections and Infestations
  - Upper respiratory tract infection 439 (13.7) 391 (12.3)
  - Nasopharyngitis 414 (13.0) 381 (12.3)
- Respiratory, Thoracic And Mediastinal Disorders
  - Cough 136 (4.3) 109 (3.4)
  - bronchitis 111 (3.5) 90 (2.9)
- Skin And Subcutaneous Tissue Disorders
  - Rash 67 (2.1) 58 (1.8)

Table 1. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients with Diabetes Mellitus

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>264 (8.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>207 (6.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>186 (5.8)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>169 (5.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>122 (3.8)</td>
</tr>
<tr>
<td>General Disorders And Administration Site Conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>229 (7.2)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>439 (13.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>414 (13.0)</td>
</tr>
<tr>
<td>Respiratory, Thoracic And Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>136 (4.3)</td>
</tr>
<tr>
<td>bronchitis</td>
<td>111 (3.5)</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>67 (2.1)</td>
</tr>
</tbody>
</table>

Table 2. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (9.4)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>29 (10.1)</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>270 (8.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>207 (6.5)</td>
</tr>
<tr>
<td>Musculoskeletal And Connective Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>201 (6.3)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>65 (2.0)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>53 (1.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>270 (8.5)</td>
</tr>
<tr>
<td>Respiratory, Thoracic And Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>136 (4.3)</td>
</tr>
<tr>
<td>bronchitis</td>
<td>111 (3.5)</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>67 (2.1)</td>
</tr>
</tbody>
</table>

(Table continues)
Cognitive Impairment. In clinical trials of at least 1-year duration, adverse reactions related to cognitive impairment (e.g., difficulty with concentration/attention, difficulty with memory, and confusion) were seen in patients taking BELVIQ and 0.7% of patients taking placebo.

Psychiatric Disorders. Psychiatric disorders leading to hospitalization or drug withdrawal occurred more frequently in patients treated with BELVIQ (2.2%) as compared to placebo (1.1%) in non-diabetic patients.

Euphoria. In short-term studies with healthy individuals, the incidence of euphoric mood following supratherapeutic doses of BELVIQ (40 and 60 mg) was increased as compared to placebo. In clinical trials of at least 1-year duration in obese patients, euphoria was observed in 0.17% of patients taking BELVIQ and 0.03% taking placebo.

Depression and Suicide. In trials of at least one year in duration, reports of depression/mood problems occurred in 2.8% of BELVIQ-treated patients vs. 4.0% of placebo patients. Among patients taking BELVIQ, suicide-related events occurred in 0.5% of placebo patients vs. 0.0% of patients taking BELVIQ.

Hemoglobin. In clinical trials of at least 1-year duration, 10.4% of patients taking BELVIQ and 9.3% taking placebo had hemoglobin below the lower limit of normal at some point during the trials. Anemia, defined as a decrease in hemoglobin greater than or equal to 65 mg/dL, and with symptoms occurred in 19 (7.4%) BELVIQ-treated patients and 16 (6.3%) placebo-treated patients.

Obstetric Use. In clinical trials of at least 1-year duration, obstetric reactions related to cognitive impairment (e.g., difficulty with concentration/attention, difficulty with memory, and confusion) were seen in patients taking BELVIQ and 0.7% of patients taking placebo.

Psychiatric Disorders. Psychiatric disorders leading to hospitalization or drug withdrawal occurred more frequently in patients taking BELVIQ (2.2%) as compared to placebo (1.1%) in non-diabetic patients.

Euphoria. In short-term studies with healthy individuals, the incidence of euphoric mood following supratherapeutic doses of BELVIQ (40 and 60 mg) was increased as compared to placebo. In clinical trials of at least 1-year duration in obese patients, euphoria was observed in 0.17% of patients taking BELVIQ and 0.03% taking placebo.

Depression and Suicide. In trials of at least one year in duration, reports of depression/mood problems occurred in 2.8% of BELVIQ-treated patients vs. 4.0% of placebo patients. Among patients taking BELVIQ, suicide-related events occurred in 0.5% of placebo patients vs. 0.0% of patients taking BELVIQ.

Hemoglobin. In clinical trials of at least 1-year duration, 10.4% of patients taking BELVIQ and 9.3% taking placebo had hemoglobin below the lower limit of normal at some point during the trials. Anemia, defined as a decrease in hemoglobin greater than or equal to 65 mg/dL, and with symptoms occurred in 19 (7.4%) BELVIQ-treated patients and 16 (6.3%) placebo-treated patients.

Obstetric Use. In clinical trials of at least 1-year duration, obstetric reactions related to cognitive impairment (e.g., difficulty with concentration/attention, difficulty with memory, and confusion) were seen in patients taking BELVIQ and 0.7% of patients taking placebo.
Surgical Options

Indications
Patients with a BMI >35 kg/m² with obesity-related comorbidities, and those with a BMI >40 kg/m² with or without comorbidities are currently eligible for bariatric surgery (Figure 2).1

Figure 2 Candidates for Bariatric Surgery

- BMI >40 kg/m², or BMI >35 kg/m² with significant obesity-related comorbidities
- Acceptable operative risk
- Documented failure of nonsurgical weight-loss programs
- Psychologically stable, with realistic expectations
- Well-informed and motivated patient
- Supportive family and social environment
- Absence of active alcohol or substance abuse
- Absence of uncontrolled psychotic or depressive disorder

BMI, body mass index.

For a patient to be appropriate for bariatric surgery he or she must have attempted a medical weight-loss program and should be highly motivated to make postsurgical lifestyle changes. In 1991, the National Institutes of Health (NIH) guidelines recommended that bariatric surgery be limited to patients aged 18 to 60 years. At that time, there was insufficient evidence to make recommendations about surgery for patients at the extremes of age. Although advanced age has been a predictor of increased mortality after bariatric surgery in some studies,13,14 there is evidence from case studies that bariatric surgery can be safe and effective in carefully selected adolescent and older patients.

Contraindications
Patients who cannot tolerate general anesthesia because of cardiac, pulmonary, or hepatic insufficiency are not candidates for surgery. Additionally, patients must be able to understand the consequences of the surgery and comply with the extensive preoperative evaluation and postoperative lifestyle changes, diet, vitamin supplementation, and follow-up program. Patients who have ongoing substance-abuse issues or unstable psychiatric illness are also poor candidates.
Follow-up

Bariatric surgery patients require lifetime follow-up. Early postoperative visits focus on potential complications or difficulties and the dramatic changes in dietary habits. Later follow-up visits focus on psychological support, nutritional assessment and vitamin supplementation, and adherence to an exercise program. Patients who present with new-onset abdominal pain, vomiting, or gastroesophageal reflux months to years after bariatric surgery should be referred to a bariatric surgeon. These symptoms may result from an anastomotic ulcer or stricture, or an intermittent bowel obstruction after Roux-en-Y gastric bypass (RYGB). Following laparoscopic adjustable gastric banding (LAGB), a new onset of gastroesophageal reflux or dysphagia may suggest gastric prolapse through the band. A patient who exhibits these signs requires prompt evaluation and treatment.

Procedures

Roux-en-Y Gastric Bypass. RYGB combines a restrictive component and a limited proximal intestinal bypass, and is the most common bariatric procedure performed in the U.S. (80% of all bariatric procedures). Most RYGB procedures are now performed laparoscopically, resulting in faster recovery and fewer pulmonary and wound complications when compared with open surgery. A small, 15- to 30-mL gastric pouch is created to restrict food intake, and a Roux-en-Y anastomosis bypasses the duodenum and proximal jejunum (about 150 cm). The risks and benefits associated with RYGB are shown in Figure 3. RYGB results in superior weight loss and comorbidity resolution with excellent long-term excess weight loss (EWL) of 50% to 55% after 10 years. RYGB has unique effects on gut hormones and glucose homeostasis that are weight-loss independent. These incretin effects and a rapid improvement in diabetes have been observed in patients with mild, moderate, and severe obesity.

Laparoscopic Adjustable Gastric Banding. The first device for laparoscopic adjustable gastric banding (LAGB) was approved for use in the U.S. in 2001 after demonstrating excellent results in Europe and Australia. In this procedure, a silicone band with an inflatable inner collar is placed around the upper portion of the stomach to create a small gastric pouch and to restrict the gastric cardia. The band is connected to a port that is placed in the subcutaneous tissue of the abdominal wall. The inner diameter of the band can be adjusted by injecting saline through the port.

The adjustability of LAGB is a major advantage over vertical-banded gastroplasty. Band adjustments are made according to weight loss, hunger, and satiety by injecting or removing saline via the subcutaneous port. Severe complications and mortality rates are lower for LAGB than for RYGB, but LAGB typically results in less weight loss that occurs more gradually. Common risks and benefits of LAGB are shown in Figure 4.
**Figure 3 Risks and Benefits of Roux-en-Y Gastric Bypass**

**Laparoscopic Roux-en-Y Gastric Bypass**

**Risks:**
- 1-2% anastomotic leak rate
- 2-15% anastomotic ulcer/stricture rate
- 1-5% late bowel obstruction rate
- 0.16% mortality rate

**Micronutrient deficiencies** (iron, B12, calcium, vitamin D), if not supplemented and followed long-term

**Benefits:**
- 65-80% excess weight loss
- 84% resolution of diabetes
- 97% improvement in hyperlipidemia
- 68% resolution of hypertension
- 78% resolution of sleep apnea

**Figure 4 Risks and Benefits of Laparoscopic Adjustable Gastric Banding**

**Laparoscopic Adjustable Gastric Banding**

**Risks:**
- 2-25% slippage/eruption rate
- 0-2% band erosion rate
- 20-40% inadequate weight loss
- 15-30% late re-operation rate for failures/complications

**Benefits:**
- 40-60% excess weight loss
- 55% resolution of diabetes
- 60% improvement in hyperlipidemia
- 45% resolution of hypertension
- 95% resolution of sleep apnea
Sleeve Gastrectomy. Laparoscopic sleeve gastrectomy (LSG) has been used as a weight-loss procedure in a variety of patient groups for more than 10 years. The risks and benefits of this procedure are described in Figure 5. This operation involves a vertical resection and removal of the body and fundus of the stomach, leaving a tubular gastric lumen from the gastroesophageal junction to the antrum. The pylorus is left intact and there is no device or bypass associated with this procedure. Initially, LSG was used as part of a risk-management strategy for high-risk and very high BMI patients. After achieving substantial weight loss and improved health status following LSG, these patients underwent an RYGB or duodenal switch procedure to continue the weight loss. In the past several years, LSG has gained acceptance as a primary bariatric procedure for lower BMI patients, as well. Early complications include leaks at the gastric staple line in 1% to 2% of patients, bleeding, and strictures or narrowing at the gastric incisura. The re-operation and late complication rates for LSG are lower than for LAGB and RYGB, but overall LSG has been shown to fall between LAGB and RYGB in terms of risks, benefits, and weight loss.

Figure 5 Risks and Benefits of Laparoscopic Sleeve Gastrectomy

<table>
<thead>
<tr>
<th>Risks:</th>
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<tbody>
<tr>
<td>1-2% leak rate</td>
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<tr>
<td>1-2% stenosis/stricture rate</td>
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<tr>
<td>20-30% incidence of GERD long-term</td>
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<tr>
<td>5% re-operation rate</td>
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<tr>
<td>0.1% mortality rate</td>
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<table>
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<tr>
<th>Benefits:</th>
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<tr>
<td>50-60% excess weight loss long-term (&gt;5 years)</td>
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<tr>
<td>50-60% remission of diabetes</td>
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<tr>
<td>75% remission of sleep apnea</td>
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<tr>
<td>60-75% remission hypertension</td>
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Biliopancreatic Diversion. Biliopancreatic diversion is a malabsorptive procedure performed by less than 3% of bariatric surgeons in the U.S. This procedure is designed to limit intestinal energy absorption to the length of the distal common channel. Although these procedures offer the best and most durable weight-loss results of any bariatric procedure performed today, higher complication rates, nutritional deficiencies, and a higher mortality rate have limited their widespread use.

Outcomes

In a meta-analysis of 29 studies of the drug orlistat (also called tetrahydrolipstatin), the pooled mean weight loss for orlistat-treated patients was 2.59 kg at 6 months and 2.89 kg at 12 months. The average age of patients enrolled was 48 years, and the average BMI was 36.7 kg/m².

Other agents—such as phentermine, diethylpropion, and fluoxetine—result in a 3.0- to 3.6-kg weight loss after 1 year when used in combination with lifestyle modifications. There are limited data on sertraline, bupropion, topiramate, and zonisamide with regard to weight-loss outcomes. Therefore, recommendations cannot be made until further studies have been completed.
A randomized, controlled trial evaluating the use of the laparoscopic adjustable gastric band (lap-band) for mild to moderate obesity (BMI 30 kg/m$^2$ to 35 kg/m$^2$) has demonstrated significantly greater weight loss and comorbidity resolution among patients in the surgical group compared with those enrolled in an aggressive medical weight-loss program. After 2 years, EWL was 87% in the surgical group and 21% in the nonsurgical group. Metabolic syndrome resolved in 93% of surgical patients and in 47% of nonsurgical patients.17

A large, prospective, matched cohort study (Swedish Obese Subjects Study) demonstrated the durability of weight loss and comorbidity reduction 10 years after bariatric surgery18 and a 30% reduction in all-cause mortality in the surgery group.19 Another large, matched cohort study demonstrated a significant reduction in mortality (40% reduction in all-cause mortality) 7 years after gastric-bypass surgery.20

A meta-analysis analyzing 22,094 patients in 136 studies found that for all bariatric procedures, the average EWL was 61.2%. Bilopancreatic diversion or duodenal switch procedures had the highest overall EWL (70%), followed by gastric bypass (61%), and gastric banding (47%). Overall, diabetes improved or resolved in 86% of patients, hyperlipidemia improved in 70%, hypertension improved or resolved in 78.5%, and obstructive sleep apnea improved or resolved in 83.6% of patients.21 Two recent randomized controlled trials have demonstrated the efficacy of bariatric surgery over medical therapy for the treatment of type 2 diabetes, often eliminating the need for hypoglycemic and cardiovascular drugs.22,23

In a meta-analysis of more than 85,000 patients, the overall postoperative mortality after bariatric surgery (<30 days) was 0.3%. The operative mortality rates for laparoscopic restrictive procedures and laparoscopic gastric bypass were 0.07% and 0.16%, respectively.24 Mortality after bariatric surgery is primarily the result of pulmonary embolism, anastomotic leak, or septic complications.

**Summary**

- Severe obesity can adversely affect every organ system.
- Detailed evaluation of symptoms can uncover serious comorbidities.
- Diabetes, cancer, and cardiovascular disease are common in obese patients.
- Central adiposity is associated with the presence of the metabolic syndrome.
- All obese patients (BMI >30 kg/m$^2$) should be counseled on lifestyle and behavioral modifications, such as appropriate diet and exercise.
- Pharmacologic therapy can be offered to obese patients who have failed to lose weight through exercise and changes in diet.
- Bariatric surgery should be considered for morbidly obese patients in whom medical weight loss programs—diet and exercise, with or without pharmacotherapy—have failed. Patients with a BMI >40 kg/m$^2$, or >35 kg/m$^2$ with obesity-related comorbidities, are candidates for bariatric surgery.
- Bariatric surgery should be considered for the treatment of type 2 diabetes in severely and moderately obese individuals.
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