DRUG TREATMENTS IN OBESITY

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Pharmacist Learning Objectives:
1. Describe three tools used to help measure degree of obesity.
2. Explain the function of adipose tissue and the hormones involved with it.
3. Describe two strategies for weight loss and maintenance.
4. Identify the most common weight-loss medications and the side effects of each.

INTRODUCTION
Obesity is defined as a condition characterized by the excessive accumulation and storage of fat in the body. Being overweight or obese are both conditions where extra fat is present, however the degree of excess fat differs between the two states. Being overweight is characterized as having a body mass index (BMI) in the range of 25-29.9 kg/m², while being obese is described as a BMI ≥30 kg/m². Obesity is a medical condition that affects more than one-third (35.7%) of adults and approximately 17% of children and
adolescents in the United States. The incidence of obesity has been increasing in the United States over the last several decades.

Obesity and its related co-morbidities carry a significant economic burden on the U.S. health care system. Not only can obesity result in direct medical costs, including preventive, diagnostic, and treatment related costs, it can also involve indirect medical costs relating to morbidity and mortality. Indirect medical costs correlate with income loss, decreased productivity, and absenteeism. In 2008, obesity related medical costs were estimated at an astounding $147 billion. Additionally, for persons with a BMI ≥30 kg/m², relative mortality rates (especially from cardiovascular disease) are increased by 50 to 100 percent above that of people with a BMI in the range of 20-25 kg/m².

Trends in obesity can change based upon several different factors, including: geographical region, race, and socioeconomic status. As of 2010, no state in the U.S. had a prevalence of obesity that was less than 20 percent. States with the highest percentage of obese people (≥30% of population) include: Mississippi, West Virginia, Alabama, Louisiana, Kentucky, South Carolina, Tennessee, Michigan, Texas, Arkansas, Missouri, and Oklahoma. U.S. states with the lowest percentage of obese people (20-24% of population) include: Hawaii, California, Colorado, Connecticut, District of Columbia, Massachusetts, Montana, Nevada, New Jersey, New York, Utah, and Vermont. The region of the United States with the highest prevalence of obesity is the South with 29.4%, followed by the Midwest at 28.7%, the Northeast at 24.9%, and lastly, the West at 24.1%. Obesity trends can also vary by race and socioeconomic status. Non-Hispanic blacks have the highest rate of obesity (44.1%), followed by Mexican-Americans (39.3%), all Hispanics (37.95%), and non-Hispanic whites (32.6%). There is no significant relationship between obesity and education among men; however, in women, those with college degrees are less likely to be obese compared with less educated females, respectively.

Energy balance, or calorie balance, is the cornerstone of any healthy lifestyle. The amount of calories consumed through eating and drinking should be balanced with the calories burned through physical activity. Roughly 70 percent of calories burned throughout the day are due to activities like breathing, digesting food, and one’s daily routine. Calorie balance is more important over time, and not as important on a daily basis. Maintaining an energy balance over long periods of time helps to control weight gain.

Obesity can be a result of a variety of factors including genetics, metabolism, hormones, behavior, environment, culture, and socioeconomic status. Environmental influences specifically consist of a person’s food intake and physical activity. In the United States, there is a wealth of calorie-dense, inexpensive, appetizing food. Adding to the problem is that physical activity among many Americans is insufficient to balance their calorie intake. Many people in the U.S. are limited to sedentary habits at home, as well as in the workplace. Hormonal regulation is another important component of obesity occurrence and progression. Adipose tissue is an active endocrine organ that creates and secretes biologically active substances. Major hormones involved with adipose tissue include: adiponectin, leptin, pro-inflammatory cytokines, C-reactive protein, among others. Leptin and adiponectin play a
key role in metabolism. Leptin is a centrally acting hormone that is involved in appetite regulation and regulating feeding behavior. Levels of leptin are generally high in obese patients. Adiponectin has a wide assortment of metabolic and anti-inflammatory actions and is down regulated in obese patients, unlike leptin. Causes of obesity in each patient is individualized and multi-factorial.

**Tools to Assess Obesity**

There are a variety of tools that can help to measure degree of obesity and are helpful to determine success of therapy. These tools include:

- **Body Mass Index (BMI):** BMI is a routine measurement for obesity in adults. BMI is a measure of body fat based on the height and weight. BMI does not actually measure the percentage of body fat or regional fat distribution. This tool has long been used to categorize patients in the underweight, normal weight, overweight, obese, and morbidly obese. BMI is a fairly reliable indicator of body fat for most adults, with the exception of athletes and the elderly. The BMI tool may overestimate fat content in athletes and muscular individuals and underestimate fat content in elderly people who have lost muscle mass. Body mass index is not an indicator of overall health nor an agent to help determine cardiovascular risk factors. Patients who fall within the normal BMI category are not necessarily healthy. It is still important for patients with a normal BMI to eat a balanced diet and get regular exercise.

- **Waist Circumference:** Waist circumference positively correlates with the amount of abdominal fat present. The existence of extra abdominal fat is a strong and independent predictor for adverse cardiovascular risk factors, unlike BMI. Men and women with a waist circumference >40 inches and >35 inches, respectively, have an increased risk of development of obesity-related co-morbidities. The categorization of disease risk based off of BMI and waist circumference is located in Table 1.

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### Table 1. Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Men ≤40 inches</th>
<th>Men &gt;40 inches</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Women ≤35 inches</td>
<td>Women &gt;35 inches</td>
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</tbody>
</table>
### Waist-to-Height Ratio

The waist-to-height ratio is simply one’s waist measurement divided by one’s height. According to a recent meta-analysis, the weight-to-height ratio has 4 to 5% better discriminatory power to detect obesity-related adverse outcomes compared with BMI. This ratio gives a more accurate assessment of overall health because the most dangerous place to carry fat is in the abdomen.

### Measurement of Risk Status

Categorizing the patient’s risk for obesity-related morbidity and mortality is also an important step. Table 2 displays the steps in risk stratification.

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>BMI Range</th>
<th>Waist-to-Height Ratio</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
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</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td>--</td>
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</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
<td>High</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0-34.9</td>
<td>I</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>Very High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>Extremely High</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>≥40.0</td>
<td>III</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

*Disease Risk for type 2 diabetes, hypertension, and CVD
Table 2.

<table>
<thead>
<tr>
<th>RISK ASSESSMENT FOR CARDIOVASCULAR DISEASE³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1: Identify cardiovascular risk factors</strong></td>
</tr>
<tr>
<td>If an obese patient has ≥2 factors listed, there is an increased risk of developing an obesity-related disorder:</td>
</tr>
<tr>
<td>• Elevated LDL cholesterol (above goal)</td>
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<tr>
<td>• Hypertension (BP ≥140/90 mmHg) or on hypertensive medications</td>
</tr>
<tr>
<td>• HDL ≤40 mg/dL</td>
</tr>
<tr>
<td>• Cigarette smoking</td>
</tr>
<tr>
<td>• Family History of coronary heart disease</td>
</tr>
<tr>
<td>• Increased age of patient</td>
</tr>
<tr>
<td>• Impaired fasting glucose</td>
</tr>
<tr>
<td><strong>STEP 2: Identify patients at a very high risk of mortality</strong></td>
</tr>
<tr>
<td>Aggressive therapy will be needed if these conditions exist:</td>
</tr>
<tr>
<td>• Established coronary heart disease (history of myocardial infarction, angina pectoris, coronary artery surgery/procedures)</td>
</tr>
<tr>
<td>• Presence of atherosclerotic diseases (peripheral artery disease, abdominal aortic aneurysm, carotid artery disease)</td>
</tr>
<tr>
<td>• Type II diabetes</td>
</tr>
</tbody>
</table>

**Obesity and Cardiovascular Risk**

All overweight and obese patients with a BMI ≥25 are considered at risk for developing associated co-morbidities, including: hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and certain cancers.³ The development of diabetes and subsequent insulin resistance is a consequence of the body’s adipose tissue altering insulin action through the secretion of pro-inflammatory cytokines.⁶ Additionally, there is an increase in glucose production and decreased glucose uptake into cells. These factors all contribute to insulin resistance and the development and progression of type II diabetes. Obesity also has a strong effect on lipoprotein metabolism.⁶ There is an overproduction and decreased clearance of VLDL (very-low density lipoprotein) molecules. There can also be increases in the distribution and constitution of LDL (low-density lipoprotein) particles, and a down-regulation of HDL (high-density lipoprotein) molecules. Together, these effects on lipid production and metabolism can significantly promote pro-inflammatory and pro-atherosclerotic conditions, contributing to
The incidence of hypertension is three times higher among obese adults versus healthy weight individuals. Over-stimulation of the sympathetic nervous system and the renin-angiotensin system are the main causes of high blood pressure in obese people. The hemodynamic changes seen with high blood pressure in obese patients can lead to left ventricular dystrophy. Additionally, the accumulation of lipid particles in the myocardial vasculature significantly increases the risk of myocardial infarction morbidity or mortality. In conclusion, the presence of co-morbidities should be considered when deciding treatment options.

**General Approach to Treatment**

The first step in the approach to treating obesity is to measure the patient’s weight, height, and waist circumference, then calculate his or her BMI. If the patient has a BMI ≥25 kg/m² or waist circumference >40 inches (for males) and >35 inches (for females), then assess the patient’s risk factors. If the patient has ≥2 risk factors, the clinician and the patient should devise goals and treatment strategies for weight loss and risk factor control. If the patient does not have at least 2 risk factors present, yet they desire/need to lose weight, they should also devise goals and treatment strategies. Progress should be monitored and the patient should be counseled on dietary therapy, behavior modification, and physical activity.

**Efficacy of Weight Loss Therapy in Clinical Trials**

The efficacy of prescription medications used to combat obesity is based on the 2007 FDA guidance on developing products for weight management. Those requirements are:

- The difference in mean weight loss between the active treatment group and placebo is at least 5%, and the difference is statistically significant.
- The proportion of patients who lose ≥5% of their baseline body weight in the active treatment group is at least 35% of the total sample and is approximately double the proportion in the placebo group. The difference between the active and placebo groups must also be statistically significant.

**Goals for Weight Loss and Management**

The initial goal for weight loss is to reduce body weight by 10% from baseline. The rationale for this goal is that moderate weight loss can considerably reduce the severity of obesity-related morbidities and risk factors. More weight loss can be attempted after this goal is reached. A reasonable time line should be instituted, a realistic time period is 6 months to reach the initial goal and equals about a 1 to 2 pounds of weight loss per week. Patients should be instructed that permanent weight loss constitutes indefinite dietary, behavioral, and activity level changes. Evidence suggests that better weight control is achieved with at least 6 months of intervention.

**Strategies for Weight Loss and Maintenance**

**Dietary modifications:** Changing the patient’s diet is an essential component of a weight loss program. The caloric intake should be decreased by 500 to 1,000 kcal per day. Guidelines recommend the best diet for weight loss and maintenance is a low-calorie diet (LCD). The components of a LCD can be found in Table 3. LCD can reduce total body weight by an average of 8% over 3 to 12 months. Very low-calorie
diets (VLCD) produce greater initial weight loss versus LCDs but long term weight loss (>1 year) is not different from that of LCD. In addition to restricted calories, the patient should also evaluate what they are eating to make sure their diet is balanced in all food groups. The patient should also maintain adequate water intake and minimize alcoholic beverage consumption.

Table 3.

<table>
<thead>
<tr>
<th>LOW CALORIE DIET RECOMMENDATIONS&lt;sup&gt;3&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>Approximately 500 to 1,000 kcal/day reduction from usual intake</td>
</tr>
<tr>
<td>Total Fat</td>
<td>30% or less of total calories</td>
</tr>
<tr>
<td>Saturated Fatty Acids</td>
<td>8-10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated Fatty Acids</td>
<td>Up to 15% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated Fatty Acids</td>
<td>Up to 10% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;300 mg/day</td>
</tr>
<tr>
<td>Protein</td>
<td>Approximately 15% of total calories</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>55% of more of total calories</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>No more than 100 mmol/day (approximately 2.4 g of sodium)</td>
</tr>
<tr>
<td>Calcium</td>
<td>1,000 to 1,500 mg</td>
</tr>
<tr>
<td>Fiber</td>
<td>20 to 30 g</td>
</tr>
</tbody>
</table>

**Physical activity:** A goal of exercising at least 30 minutes most days of the week will promote and sustain weight loss.<sup>3</sup> Guidelines state that aerobic exercise in obese adults results in modest weight loss independent of calorie intake; however, the combination of LCD and physical activity produces greater weight loss than either alone. In addition to weight loss, physical activity also promotes cardio-respiratory fitness and can improve cardiovascular risk management.

**Behavior therapy:** Principles such as reinforcement (e.g. sticking to a daily routine), overcoming barriers (e.g. identifying weight loss weaknesses and consciously working to overcoming them), self-monitoring (e.g. calorie counting and accountability), motivation (e.g. having a supportive network of friends and family), and compliance with weight loss targets collectively help to promote weight loss goals.<sup>3</sup> This therapeutic strategy is best used in combination with the diet changes and increased activity. Guidelines state that no one behavioral therapy is superior to any other during weight loss and that the treatment that provides the highest frequency of patient and practitioner contact are the most successful.<sup>3</sup> Behavior therapy can be instituted by a variety of practitioners, including physicians, pharmacists, dieticians, etc. Changing a person’s knowledge, motivation, behavioral management skills, routine, and flexibility all need to be accomplished for maximal weight loss results.
Pharmacotherapy: Instituting drug therapy can be another tool to achieve weight loss. A variety of medications can be selected to help enhance weight loss, improve behavioral modifications, and help treat co-morbidities. Weight loss medications should only be used as part of a comprehensive weight loss program, and never alone. It is recommended that drug therapy be instituted when BMI is \( \geq 30 \text{ kg/m}^2 \) or when BMI is between 27 and 29.9 kg/m\(^2\) with a major obesity related co-morbidity (e.g. hypertension, diabetes, dyslipidemia).  

PRESCRIPTION MEDICATION TO TARGET OBESITY 

The addition of prescription medication should only be used in conjugation with a comprehensive diet and exercise plan and in patients with established obesity and/or co-morbidities. Finding a satisfactory balance between safety and efficacy for anti-obesity drugs has been difficult because many drugs have failed in clinical trials or after registration.

Peripherally-Acting Medications: 

Orlistat is a lipase inhibitor that prevents absorption of dietary fat. Orlistat specifically works by bonding with gastric and pancreatic lipase enzymes located in the small intestine and stomach to prevent the catabolism of triglycerides. It has minimal systemic absorption, making it a relatively safe drug. Orlistat was first approved in the United States by the FDA in April of 1999 as Xenical®. Xenical® is available as prescription only, with no therapeutic equivalents. It is manufactured by Hoffman La Roche and comes in one standard dose, 120 mg. In 2007, the FDA approved the over-the-counter dose of 60 mg. The over-the-counter strength, named Alli®, is manufactured by GlaxoSmithKline. Both doses are recommended to be used three times a day. Orlistat has an FDA-labeled indication for the treatment of obesity in conjugation with a reduced-calorie diet and appropriate exercise; it is approved for patients with a BMI \( \geq 30 \text{ kg/m}^2 \). It is the only anti-obesity drug FDA-approved for long-term use. Additionally, orlistat has an off-label indication for the treatment of hyperlipidemia. In several clinical trials, orlistat, in addition to diet, promoted weight loss significantly more than diet alone.

Not only did patients taking orlistat experience more weight loss, they were also able to maintain their weight loss more so than the placebo group. In the landmark XENDOS study that randomized over 3,000 patients, orlistat was proven to be more effective at producing weight loss than placebo (average weight loss: -5.8 kg versus -3.0 kg, \( P<0.001 \)). This study showed that orlistat can produce significant weight loss, with an expected weight loss of 5-10% of weight. In addition to having efficacy in weight loss, orlistat has demonstrated benefit in decreasing the incidence of cardiovascular risk factors, including decreasing diabetes incidence and improving lipid control. Surrogate markers for cardiovascular disease, such as fasting blood glucose, HbA1c, total cholesterol, and LDL cholesterol have all been better controlled with orlistat and exercise, versus placebo and exercise.

It is recommended that orlistat be taken during or up to one hour after eating a fat-containing meal. If a meal is omitted, the dose of orlistat can also be skipped. Because orlistat decreases the absorption of dietary fats, it is recommended that patients taking this medication take a vitamin supplement containing fat-soluble vitamins.
Orlistat is generally well-tolerated and has a small number of contraindications, adverse drug interactions, and drug interactions. If patients experience any of these contraindications, he/she should completely avoid this medication: cholestasis (blocked bile flow from liver), chronic malabsorption syndrome, pregnancy, or hypersensitivity to orlistat. The major adverse drug reactions reported are: gastrointestinal events (oily spotting, abdominal discomfort, flatulence with discharge, fecal urgency, oily stool). Other side effects include: headache, back pain, upper respiratory infection, and foot edema. Orlistat also has several drug interactions, mainly due to its mechanism of action. The most pertinent drug interaction includes decreasing the absorption of fat-soluble vitamins, including vitamins A, D, E and K. The decreased absorption of vitamin K can have severe consequences if a patient is taking concurrent warfarin. The combination of the vitamin K antagonism by warfarin and decreased absorption of vitamin K absorption can increase bleeding. Major drug interactions are also seen when orlistat is used concomitantly with cyclosporine or levothyroxine. Orlistat can decrease concentrations of both of these medications, and doses of each should be separated by at least 3-4 hours. 

**Centrally-Acting Medications:**

Phentermine hydrochloride, diethylpropion hydrochloride, benzphetamine hydrochloride and phendimetrazine tartrate are all sympathomimetic amines similar to the class of medications known as the amphetamines. These anorexiants work centrally to suppress appetite by stimulating the hypothalamus to cause norepinephrine release. All of the medications in this class are scheduled because of their abuse potential in patients. Table 4 summarizes the medications in this class.

---

**Table 4**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Phentermine</th>
<th>Diethylpropion</th>
<th>Benzphetamine</th>
<th>Phendimetrazine</th>
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</thead>
<tbody>
<tr>
<td><strong>Brand</strong></td>
<td>Adipex-P®</td>
<td>Tenuate®</td>
<td>Didrex®</td>
<td>Bontril®</td>
</tr>
<tr>
<td></td>
<td>Suprenza™</td>
<td>Tenuate Dospan®</td>
<td></td>
<td>Bontril PDM®</td>
</tr>
<tr>
<td><strong>Original FDA Approval</strong></td>
<td>1959</td>
<td>1959</td>
<td>1960</td>
<td>1976</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>IV</td>
<td>IV</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
<td>Adipex-P®: 15 mg and 20 mg tablets</td>
<td>Tenuate®: 25 mg tablets</td>
<td>Didrex®: 50 mg</td>
<td>Bontril®: 105 mg ER capsule</td>
</tr>
<tr>
<td></td>
<td>Adipex-P®: 37.5 mg capsules</td>
<td>Tenuate Dospan®: 75 mg tablets</td>
<td>Bontril PDM®: 35 mg tablet</td>
<td></td>
</tr>
</tbody>
</table>
**Dosage**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Tenuate®: three times daily</th>
<th>Tenuate®: once daily</th>
<th>Didrex®: initially dosed at 25 mg to 50 mg once daily, titrated to a short term maintenance dose of 25 mg to 50 mg once to three times daily.</th>
<th>Bontril®: 105 mg daily</th>
<th>Bontril PDM®: 35 mg two to three times daily</th>
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<tbody>
<tr>
<td>Once daily</td>
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<tr>
<td></td>
<td></td>
<td>Tenuate®: once daily</td>
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<tr>
<td>Tenuate Dospan®</td>
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**Pregnancy Category**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Tenuate®: three times daily</th>
<th>Tenuate®: once daily</th>
<th>Didrex®: initially dosed at 25 mg to 50 mg once daily, titrated to a short term maintenance dose of 25 mg to 50 mg once to three times daily.</th>
<th>Bontril®: 105 mg daily</th>
<th>Bontril PDM®: 35 mg two to three times daily</th>
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<tbody>
<tr>
<td>Adipex-P®: C</td>
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<tr>
<td>Suprenza™: X</td>
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**Comments**

Phentermine was originally approved as a resin base in 1959, where phentermine hydrochloride was approved in 1973. Phentermine differs from Tenuate® only in that it is the controlled released version; efficacy is similar. Bontril® is the extended release formulation of phendimetrazine and Bontril PDM® is the immediate release formulation.

Phentermine, diethylpropion, benzphetamine, and phendimetrazine all have an FDA-labeled indication for the treatment of obesity as a short-term adjunct in obese patients. Phentermine is the most commonly used appetite suppressant and has been shown to be efficacious. In a clinical evaluation, phentermine shows 1.2 lbs per week weight loss when compared to 0.3 lbs per week seen in the placebo group between weeks three and sixteen. Phentermine also shows a statistically significant difference in weight loss versus placebo in a meta-analysis. The average weight loss in the meta-analysis study was 3.6 kg (95% CI 0.6 to 6.0 kg) at six months of therapy. Several contraindications exist for the use of these stimulants including: advanced arteriosclerosis, hyperthyroidism, pulmonary hypertension, glaucoma, severe hypertension, history of drug abuse, or use of an MAO inhibitor within 14 days. It is imperative that patients taking monoamine oxidase inhibitors, thioridazine, tricyclic antidepressants, or amphetamine-like drugs avoid concurrent use of centrally acting stimulants due to the synergistic actions of vasoconstriction when combined. There are several common, as well as, serious adverse drug reactions that all patients should be aware of upon use of any of these agents. Common adverse events of these agents include insomnia and excitability; therefore, they should be taken in the morning. Other side effects include: increased blood pressure and tachycardia (becomes serious when the elevation in blood pressure is significant), headache, blurred vision, rash, dry mouth, abdominal discomfort, nausea, vomiting, and rare psychotic episodes. Additionally, none of the central stimulants are approved for long-term treatment for obesity. These medications should only be used for up to one month due to the risk of tolerance.

Recent guidelines became effective in January of 2012 for the prescribing of controlled substances as weight loss therapy according to the Alabama Board of Medical Examiners. The purpose of these regulations is to establish a standard for physicians to appropriately prescribe...
scheduled drugs for weight reduction. These regulations allow only schedules III, IV, or V to be used for obesity. Therefore, schedule II substances should not be used, including methamphetamine (Desoxyn®) which has an indication for weight loss. The new standards do not allow controlled substance prescriptions to be phoned into a pharmacy; however, electronic versions are acceptable. In addition, each prescription should not exceed thirty-five days of therapy. The physician should follow-up with the patient monthly for observations and additional prescribing. Also, the physician must discontinue the patient’s therapy if any of the following occur: patient becomes pregnant, does not comply with physician recommendations, abuses the prescription, becomes tolerant, develops alcohol or drug abuse, or does not progress to the weight loss goals set.

**SURGICAL OPTIONS THAT TARGET OBESITY**

Surgical options are available for obese patients, but are more commonly used in morbidly obese patients with a BMI greater than 40 kg/m² or greater than 35 kg/m² in patients with co-morbidities relating to obesity. These bariatric surgical options include Roux-en-Y gastric bypass, adjustable gastric banding, and sleeve gastrectomy. Surgery is considered to be the most effective weight reduction intervention available for obese patients with an overall weight reduction of 35 to 40%; however, there are risks associated with surgery including infection, leakage, malabsorption, thromboembolism, the need for additional operations, or dumping syndrome. Although there are several possible risks, there are benefits to bariatric surgery including weight loss that leads to better health. For example, co-morbidities associated with obesity will likely diminish, such as diabetes mellitus, hypertension, and dyslipidemia. In addition, morbidity and mortality may be reduced post bariatric surgery.

Roux-en-Y is a malabsorptive and restrictive surgical procedure that creates a small stomach pouch where food products will bypass a majority of the stomach, the entire duodenum, and part of the jejunum. Roux-en-Y gastric bypass has shown a loss of 65 to 75% in excess weight and improvements in co-morbid disease states in 86% of diabetic patients, 79% of hypertensive patients, and 70% of hyperlipidemia patients. Gastric banding, also known as lap band surgery, is a non-permanent option in which a band is placed proximally around the stomach to cause restriction and satiety promotion. Like Roux-en-Y, weight loss occurs and co-morbidities improve; however, these improvements are not as great with the lap band procedure; which include 47.5% excessive weight loss and approximately 47.9% co-morbidity resolution. The benefit of lap band over Roux-en-Y is the lack of malabsorption. Another weight loss surgery available for obese patients is the sleeve gastrectomy. This procedure removes the curvature portion of the stomach, making the stomach tubular-shaped. This surgery should only be considered in patients with an extremely high BMI that may not benefit from Roux-en-Y bypass or laparoscopic banding. When morbidly obese patients do not benefit from decreased caloric intake, increased physical activity, and weight loss medication therapy, weight loss surgery should be considered, especially in patients at increased obesity-related mortality and morbidity.
PRESCRIPTION MEDICATIONS THAT HAVE A SIDE EFFECT OF WEIGHT LOSS

There are several drug classes that produce weight loss secondary to its primary mechanism of action. Many of these medications do not have an FDA-labeled indication for the treatment of obesity, but are being studied for such utility. **Exenatide (Byetta®)** and **liraglutide (Victoza®)** does not have an FDA indication for weight loss but have been shown to significantly decrease body weight in patients with diabetes mellitus.\(^{27-31}\) There are several trials underway for the use of exenatide and liraglutide in non-diabetic obese patients.\(^{32}\) **Metformin** only has an FDA indication for weight loss in patients who have gained weight due to anti-psychotic medications.\(^{31,33}\) Metformin has also been shown to produce sustained weight loss in obese patients with type 2 diabetes mellitus or polycystic ovarian syndrome. Another diabetic medication that promotes weight loss is **pramlintide (Symlin®)**. It does not have an FDA indication for use in weight loss; however, it has been shown to produce weight loss due to satiety.\(^{34-36}\) Another medication that promotes weight loss is **fluoxetine.** It currently does not have an FDA indication for use in weight loss.\(^{31}\) Despite this, it has been shown to reduce weight in patients with or without depression.\(^{37}\) Weight loss was not associated with GI adverse events such as diarrhea, nausea or vomiting but was associated with the increased serotonin in the medial hypothalamus that occurs due to the inhibition of reuptake. Increased serotonin in the hypothalamus decreases food intake, duration of eating, and lowers carbohydrate intake.

OVER-THE-COUNTER MEDICATIONS

There are numerous over-the-counter, non-prescription weight loss products available on the market. These dietary supplements are not under strict FDA regulation, but rather regulated by The Dietary Supplement Health and Education Act of 1994.\(^{38}\) The weight loss product ingredients are mostly herbal supplements combined with other minerals and vitamins, and are commonly used in the United States.\(^{38,39}\) According to a study published in the Journal of the American Dietetic Association, approximately 15.2% of adult patients participating had used weight loss supplements in their lifetime, and 8.7% used one or more dietary supplement within the past year.\(^{39}\)

Over the counter and herbal/natural weight reduction therapy consists of several categories, including:\(^{38}\)

- **Stimulants, energy boosters, and thermogenic aids:** bitter orange and caffeine are energy boosting stimulant weight loss ingredients used to decrease fatigue and increase metabolism.
- **Fat and carbohydrate modulators:** chromium, green tea, garcinia, brindleberry, licorice, pyruvate, and conjugated linoleic acid are considered carbohydrate and fat modulators that alter the metabolism of fat or carbohydrates to decrease fat
mass and increase muscle mass.

- **Appetite suppressants and satiety promoters:** hoodia, psyllium, plantain, guar gum, and glucomannan promote satiety and suppress appetite, resulting in a decreased intake of calories.

- **Fat and carbohydrate absorption blockers:** chitosan is considered to block fat absorption in the intestines, and ginseng is considered to block carbohydrate absorption in the intestines. Orlistat inhibits gastric enzymes in the stomach and inhibits fat absorption in the small intestines resulting in weight reduction.

- **Laxatives and diuretics:** dandelion is used as a diuretic in weight loss therapy, and cascara sagrada is used as a laxative agent in weight loss therapy.

- **Other miscellaneous products:** phosphatidylserine, theanine, and beta-sitosterol are used in weight reducing products to block cortisol, therefore, reducing appetite and decreasing fat storage. In addition, calcium, willow bark, and guggul are included in some over-the-counter weight loss supplements.

In the past, ephedra was the most commonly used supplement for weight loss in the U.S. Ephedra is no longer available due to harmful cardiovascular side effects and FDA banning. Supplements such as bitter orange are being used to replace ephedrine alkaloid products; however, cardiovascular effects are seen in this product as well. In an ephedra-free weight-loss study, cardiovascular changes were seen with an increase in blood pressure and heart rate when compared to placebo. Over-the-counter weight loss supplements are not recommended and should be used cautiously due to the lack of evidence-based safety and efficacy.

### MEDICATIONS NO LONGER ON THE MARKET

Several medications have been removed from the market in the United States due to safety concerns. **Meridia® (sibutramine)** was a commonly used weight loss agent. It is a norepinephrine and serotonin reuptake inhibitor that produces weight loss by primarily increasing satiety. Sibutramine was voluntarily removed off the United States market in 2010 due to increased risk of cardiovascular adverse events, including heart attack and stroke. The removal of sibutramine from the market was prompted by the results of the SCOUT trial (Sibutramine on Cardiovascular Outcomes). This study evaluated the long-term effects of sibutramine on the incidence of cardiovascular disease and death in 10,744 high-risk patients. This study showed that long-term use of sibutramine led to an increased risk of nonfatal myocardial infarction and nonfatal stroke.

**Pondimin® (fenfluramine) and Redux® (dexfenfluramine)** are both stimulants that increase serotonergic activity. These agents were withdrawn from the U.S. market in 1997 due to increased incidence of cardiac problems. Both are structurally related to amphetamine, with racemic dexfenfluramine having about double the
anorectic potency as fenfluramine. The widely used “phen-fen” (combination phentermine and fenfluramine) was removed from the market largely based on the results of a study that showed serious adverse effects, including pulmonary hypertension and valvular heart disease. Zimulti® (rimonabant) is an inverse agonist for the cannabinoid receptor that reduces a patient’s appetite. Despite never being marketed in the United States, it was available in other countries for weight loss until suspension in 2008 for the increased risk of serious psychiatric problems, including aggression and suicide. Sanorex® (mazindol) is an anorectic agent that suppresses appetite by modification of norepinephrine and dopamine metabolism, as opposed to serotoninergic activity. It was initially approved by the FDA in 1973 for management of obesity as a short-term adjunct. It was withdrawn from the U.S. market in 1999, but not for reasons of safety or effectiveness. Sanorex® is currently included in the “Discontinued Drug Product List” section of the FDA’s Orange Book.

**FUTURE RESEARCH**

Many different medications are currently under development in the United States and elsewhere. Most of these new developments have novel mechanisms of action and show promising results. Qnexa® is a combination product of phentermine and topiramate manufactured by Vivus Pharmaceuticals. It has undergone phase III trials, and is currently awaiting FDA approval for possible weight loss therapy. Phentermine is a sympathomimetic appetite suppressing agent, and topiramate is a weak carbonic anhydrase inhibitor and antiepileptic agent. Clinical trials of Qnexa® have shown a weight loss of approximately 9.3% of total bodyweight. Unfortunately, problematic side effects have been shown, including: tachycardia, increased cleft palette in infants, memory loss, and depression. The three phase III trials of Qnexa® include EQUATE, EQUIP, and CONQUER trials, and each of these trials show an increase in weight loss when compared to placebo. The FDA has not approved Qnexa® at this time due to probable teratogenic effects. Empatic™ is another medication seeking FDA approval for weight loss. It is a combination product of zonisamide and bupropion currently being studied. Bupropion is currently approved for depression and smoking cessation, but has a side effect of weight reduction due to increased dopamine levels secondary to appetite suppression. Zonisamide is an antiepileptic agent currently approved for seizures, but also has shown weight loss efficacy in patients. Its possible mechanism of weight loss is due to dopamine and serotonin enhancement. In a recent unpublished phase II trial, Empatic™ was shown to decrease weight more so than zonisamide monotherapy, bupropion monotherapy, or placebo. Another phase II trial looked at zonisamide/bupropion combination vs. zonisamide alone in obese women. The combination product in this small sample of obese women produced a mean -7.5% weight loss while zonisamide only group produced a mean -3.1% weight loss at the end of the 12 weeks study. Common side effects associated with Empatic™ include insomnia, headache, and nausea. Velneperit is a benzoxazole neuropeptide Y5 antagonist. Neuropeptide Y is expressed widely in the central and peripheral nervous system and modulates several different roles, including food intake, energy expenditure, mood,
anxiety. Velneperit is currently under Phase II trials and shows clinical benefit in obese patients. Another promising agent is lorcaserin (Lorqess®). It is a selective serotonin 2C agonist, which controls appetite by increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake. Lorcaserin is not yet FDA approved; however, two phase III trials have been conducted and reviewed by the FDA. These two trials did use these requirements as primary efficacy endpoints (mentioned previously) as well as looking at the proportion of patients who achieved weight loss of ≥10% of their baseline weight. Both of these trials did meet the requirements for being efficacious.

Contrave® is a combination of naltrexone SR and bupropion SR that stimulates pro-opiomelanocortin (POMC) neurons in the hypothalamus that result in decreased energy intake and increased energy expenditure. Naltrexone blocks the negative feedback loop that normally occurs on the POMC by B-endorphins due to bupropion stimulation, amplifying the effects on energy balance. Four phase III trials have been completed and reviewed by the FDA on the effectiveness of combination naltrexone/bupropion on weight loss. All four trials met the criteria for efficacy (mentioned previously); however, the 4th trial showed lower efficacy in patients with diabetes mellitus.

Another agent in the pipeline is cetilistat. It is in the same class as orlistat; both are lipase inhibitors. The safety and efficacy of cetilistat has been established in several phase II clinical trials. Use of cetilistat for weight loss produces similar effects as those seen with orlistat, but is better tolerated. Phase III clinical trials have begun in Japan. Metreleptin is a novel agent in testing. It is an analog of the human hormone leptin. This neurohormone is secreted by fat cells and plays a role in body weight. Leptin is specifically integral in the regulation of energy homeostasis, fat and glucose metabolism, and weight. Metreleptin is marketed for the treatment of diabetes and hypertriglyceridemia in patients with lipodystrophy. Metreleptin has received both orphan drug designation from the FDA, as well as, fast track designation for use in patients with lipodystrophy. Obinepitide is a synthetic analogue of two natural human hormones that target Y receptors, Y2 and Y4. This novel mechanism of action plays a role in regulation of food intake and appetite. Targeting these receptors ultimately results in decreased appetite. Injectable obinepitide is currently under phase I/phase II testing. Tesofensine is a triple monoamine reuptake inhibitor that blocks noradrenaline, dopamine, and serotonin reuptake. It is thought to cause appetite suppression. Tesofensine was originally developed specifically for Parkinson’s and Alzheimer’s disease, but reduction in weight was seen in patients taking tesofensine in clinical trials. In a phase II trial, weight loss in patients was approximately -4.5 to -10.6 kg (P <0.0001) over a twenty-four week period and was dose-dependent. Like many of the stimulant weight loss medications, cardiovascular side effects have been seen, but are not considered to be significant. Other, more common, side effects include abdominal pain, nausea, constipation, and dry mouth.

CONCLUSION

Obesity is a medical condition that affects millions of Americans. Not only does it impact the individual affected with the condition, it also places a huge burden on the health care system. The impact of
Obesity spreads across every state in the United States and has global implications as well. For patients to experience the most effective weight loss, they need to know and understand their BMI, co-morbidities, and risk factors at baseline. Additionally, the patient needs to develop an understanding of healthy eating and exercise habits, and address any motivational or behavioral limitations they are experiencing. The patient also needs to maintain long-term follow-up with their healthcare provider and track his or her success. Lifestyle modifications have provided significant results in weight reduction, but there has been an increased trend toward pharmaceutical development to help combat obesity. With new drugs in the pipeline for the treatment of obesity, the upcoming approach to weight loss will likely include a pharmacological agent, in addition to traditional methods.

The Pharmacists Education Foundation (PEF) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. To receive continuing pharmacy education (CPE) credit, pharmacists MUST COMPLETE AN ONLINE QUIZ AND EVALUATION FORM. A score of 70% or above is required to receive CPE credit. The link to the quiz can be accessed from the MEMBERS page of the IPA website at www.indianapharmacists.org. This is a free service to IPA members in 2013. Initial release date 12/17/2013. Expiration Date: 12/17/2016. Questions: Call IPA at (317) 634-4968.

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INSTRUCTIONS: This page is intended to help participants REVIEW the quiz prior to submitting their answers online. Please take the quiz online using the members section of the website.

Drug Treatments in Obesity Quiz Questions

1. In 2008, obesity related medical costs were approximately ___________.
   a. $1 billion  
   b. $240 billion  
   c. $147 billion  
   d. $500 billion

2. Which of the following combinations represents states with the highest percentage of obese people (BMI ≥30%)
   a. Mississippi, Hawaii, Montanta  
   b. Alabama, Louisiana, Oklahoma  
   c. Washington, Utah, New York  
   d. Texas, Michigan, Vermont

3. What percentage of calories is burned throughout the day without exercising in a typical adult?
   a. 20%  
   b. 45%  
   c. 60%  
   d. 70%

4. A body mass index of 27 kg/m² is classified as:
   a. Underweight  
   b. Normal weight  
   c. Overweight  
   d. Obese

5. The best tool to assess obesity is:
   a. Waist-to-height ratio  
   b. Body mass index  
   c. Waist circumference  
   d. Assessing one’s risk for cardiovascular disease

6. Which of the following is NOT considered a cardiovascular risk factor:
7. Which of the following is NOT considered a risk factor that identifies a patient at a very high risk of mortality?
   a. Hypertension  
   b. History of myocardial infarction  
   c. Coronary artery surgery or procedure  
   d. Type II diabetes

8. The diet that produces the most significant weight loss and weight maintenance is:
   a. Very low calorie diet  
   b. Low calorie diet  
   c. Low fat diet  
   d. Low carbohydrate diet

9. Which of the following centrally-acting stimulants is safest to use during pregnancy?
   a. Phentermine  
   b. Diethylpropion  
   c. Benzphetamine  
   d. Phendimetrazine

10. Adipex-P cannot be phoned in to the pharmacy from the physician’s office.
    a. True  
    b. False

11. Which one of the following Schedules of medications cannot be used for weight loss?
    a. II  
    b. III  
    c. IV  
    d. V

12. Roux-en-Y gastric bypass is more beneficial than lap band surgery due to its lack of malabsorption.
    a. True  
    b. False
13. Fluoxetine causes weight loss due to nausea and diarrhea.
   a. True
   b. False

14. Bitter orange is:
   a. Stimulant/energy booster
   b. Fat/carbohydrate modulator
   c. Appetite suppressant/satiety promoter
   d. Laxative/diuretic

15. Which one of the following medications was removed from the market NOT due to cardiac effects?
   a. Meridia (sibutramine)
   b. Pondimium (fenfluramine)
   c. Redux (dexfenfluramine)
   d. Sanorex (mazindol)

16. Which one of the following new medications currently in research has a mechanism of action of selective serotonin 2C agonism?
   a. Lorqess (lorcaserin)
   b. Contrave (naltrexone/bupropion)
   c. Cetilistat
   d. Velnepirit

17. Which of the following new medications currently in research is an analogue of two natural hormones?
   a. Tesofensine
   b. Obinepitide
   c. Velnepirit
   d. Qnexa (phentermine/topirimate)

18. The combination product of zonisamide and bupropion is:
   a. Qnexa
   b. Lorqess
   c. Contrave
   d. Empatic