Introduction: Obesity is a chronic disease that affects approximately 33% of adults in the United States.\textsuperscript{1,2} It is formally defined as a body mass index (BMI) of 30 kg/m\textsuperscript{2} or greater. Decreasing total body weight helps to reduce the risk of weight-associated comorbidities such as hypertension, diabetes, and hyperlipidemia.\textsuperscript{3,4} A combination of diet, exercise, and behavior therapy should be employed as an initial method for weight reduction and maintenance. If these treatment options fail, pharmacotherapy or bariatric surgery may be considered.

BMI versus Weight Circumference:
The BMI is a more accurate determination of obesity than total body weight because it takes into consideration an individual’s height.\textsuperscript{5} It is important to note that as BMI increases, the incidence of morbidity and mortality increases. Conditions such as type 2 diabetes, coronary heart disease, and sleep apnea confer a high absolute risk for mortality in obese individuals. Furthermore, obese patients with three or more risk factors which include smoking, hyperlipidemia, hypertension, impaired fasting glucose, family history of early cardiovascular disease, and advanced age (male $\geq$ 45 years, female $\geq$ 55 years) also have a high absolute mortality risk. Waist circumference can also be used to determine morbidity and mortality risks for normal weight patients and for those who are overweight but not considered obese. Men with waist circumferences $>$ 40 inches and women with waist circumferences $>$ 35 inches are considered to be at greater risk for diabetes, hypertension, and cardiovascular diseases due to accumulation of excess abdominal fat. Determination of weight circumference does not add further predictive value for disease risk classification in obese patients, especially those with a BMI $>$ 35 kg/m\textsuperscript{2}.

Diet: Reduced calorie, low fat diets (1,000 to 1,200 calories for women and 1,200 to 1,600 calories for men) are recommended for all patients with a BMI $>$ 25 kg/m\textsuperscript{2}. These diets should also include the current recommendations for sodium ($\leq$ 2.4 g/day), calcium (1,000 to 1,500 mg/day), and fat ($\leq$ 30% total calories/day). It is important to take personal preferences into consideration when formulating a dietary plan. Clinical evidence has not demonstrated any significant difference in weight loss at 1 year in patients on a reduced calorie diet compared with those on a very low calorie diet ($<$ 800 calories/day). Furthermore, very low calorie diets which require special monitoring and supplementation are difficult to follow and should not be routinely recommended.\textsuperscript{3} Alternatively, there are several commercially available weight loss programs (e.g., Weight Watchers\textsuperscript{®}, Jenny Craig\textsuperscript{®}, and Nutrisystem\textsuperscript{®}) which incorporate relatively easy-to-use diet plans.\textsuperscript{5}
Exercise: Moderate amounts of physical activity can help with weight loss as well as reduce the risk of heart disease. Most adults should participate in some form of aerobic exercise for at least 30 to 45 minutes a day 3 to 5 times a week. However, physical activity should be initiated slowly and the intensity increased gradually for most obese individuals. Furthermore, an exercise plan for some previously sedentary obese patients may need to be initially evaluated by a physician since cardiopulmonary testing may be necessary to determine an appropriate activity level.

Behavior Therapy: Behavior modification is a useful adjunct to diet and exercise for weight management. Specific behavioral strategies such as stress management, stimulus control, and social support are often integrated into various weight loss programs. Structured counseling sessions to help curb obesity-related behaviors such as eating fast food, skipping breakfast, and avoiding exercise are believed to be essential tools for maintaining weight loss.

Bariatric Surgery: Bariatric surgery may reduce mortality rates in severely obese patients. It can be considered in individuals with a BMI ≥ 40 kg/m² or a BMI between 35- and 39.9-kg/m² with certain risk factors (e.g., type 2 diabetes, coronary artery disease, severe sleep apnea) who are unable to lose weight by traditional means. Several types of bariatric surgical techniques which achieve weight loss by restricting oral intake and/or preventing absorption of food are available. After recovering from surgery, maintaining healthy eating habits and participating in regular physical activity help to ensure permanent weight loss.

Drug Therapy Assessment: Patients who have not successfully lost at least 1 lb per week after 6 months of lifestyle changes may qualify for drug therapy. A patient’s risk status should be considered when determining whether pharmacotherapy is an appropriate treatment choice; weight loss medications should ideally be reserved for patients with a BMI ≥ 30 kg/m² or a BMI ≥ 27 kg/m² with concomitant obesity-related risk factors. Risks and benefits should be assessed by a healthcare professional before initiation of therapy and regular follow-up is essential to assess drug safety and efficacy. Additionally, pharmacotherapy should be used as part of a treatment regimen that includes diet, exercise, and behavior modification. Some individuals do not respond to weight loss medications; if significant weight loss (at least 2 kg at 4 weeks) is not attained, further benefit is unlikely and discontinuation of drug therapy should be considered.

Pharmacologic Action of Weight Loss Medications: Appetite is regulated through complex mechanisms within the hypothalamus and other parts of the central nervous system (CNS). Neurotransmitters such as serotonin (5-HT) and norepinephrine can stimulate or depress hunger signals within the hypothalamus, thereby playing a crucial role in regulating appetite. Some pharmaceutical treatments for obesity focus on suppressing the appetite by stimulating the release of neurotransmitters. The effects of each neurotransmitter subtype on food intake are summarized in Table 1. Another pharmacological mechanism for promoting weight loss is the inhibition of lipase, an enzyme which aids in the digestion and absorption of fat.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Subtype</th>
<th>Action</th>
<th>Food Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>α₁</td>
<td>Stimulate Receptor</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>α₂</td>
<td>Stimulate Receptor</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>Stimulate Receptor</td>
<td>↓</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT₁ₐ</td>
<td>Stimulate Receptor</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>5-HT₁ᵦ</td>
<td>Stimulate Receptor</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>5-HT₂ᵦ</td>
<td>Stimulate Receptor</td>
<td>↓</td>
</tr>
</tbody>
</table>

Sympathomimetic Amines: Diethylpropion, benzphetamine, and phentermine are sympathomimetic amines (SAs) that work similarly to amphetamines. They decrease appetite by stimulating the hypothalamus to release norepinephrine in the CNS. These appetite suppressants are approved by the Food and Drug Administration (FDA) for short-term use in combination with a reduced-calorie diet and exercise plan. They should be reserved for those individuals who have not successfully responded to a combined diet and exercise regimen alone. Some contraindications associated with SA therapy include concomitant use of other anorectic agents, pulmonary hypertension, advanced atherosclerosis, hyperthyroidism, glaucoma, and severe hypertension. These CNS stimulants should not be taken within 14 days of monoamine oxidase inhibitors (e.g., selegiline, rasagiline) and should be used with caution in patients with epilepsy and hypertension.
Some SA-induced adverse reactions include palpitations, tachycardia, elevated blood pressure, restlessness, insomnia, anxiety, and psychosis. Before initiating SA pharmacotherapy, a baseline cardiac evaluation is recommended to detect preexisting valvular disease or pulmonary hypertension. If the patient is found to have a heart murmur or any valvular disease, SAs should not be initiated. These agents all have abuse potential and are classified as controlled substances; therefore, they would not be an appropriate choice for patients with a history of substance abuse.\textsuperscript{11-14}

Dosing information for select SA weight loss agents is listed in Table 2.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>BMI Requirement</th>
<th>Dose*†</th>
<th>Dosage Forms</th>
<th>Controlled Substance Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylpropion</td>
<td>Tenuate\textsuperscript{w,‡}</td>
<td>≥ 30 kg/m\textsuperscript{2}</td>
<td>25 mg three times a day</td>
<td>Immediate-release 25 mg tablets</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Tenuate Dospan\textsuperscript{w,‡}</td>
<td></td>
<td>75 mg daily (Controlled-release)</td>
<td>Controlled-release 75 mg tablets</td>
<td></td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>Didrex\textsuperscript{®}</td>
<td>≥ 30 kg/m\textsuperscript{2}</td>
<td>25-50 mg one to three times a day</td>
<td>50 mg tablets§</td>
<td>III</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Adipex-P\textsuperscript{®}</td>
<td>≥ 30 kg/m\textsuperscript{2} or ≥ 27 kg/m\textsuperscript{2} with risk factors (e.g., hypertension, diabetes, or hyperlipidemia)</td>
<td>18.75-37.5 mg daily before BF or 1-2 hours after BF or 18.75 mg twice daily or 15-30 mg daily 2 hours after BF</td>
<td>Phentermine: 15-, 30-, 37.5-mg capsules/37.5 mg tablets§ Adipex-P\textsuperscript{®}: 37.5 mg capsules/tablets§</td>
<td>IV</td>
</tr>
</tbody>
</table>

BMI=Body Mass Index  BF=breakfast  HCl=hydrochloride
*Approved for short-term use only (package inserts state “a few weeks”)
†Do not exceed maximum recommended dose; discontinue if tolerance occurs
‡Brand name product not available in the United States; Dospan\textsuperscript{®} is the Controlled-release formulation
§Tablets are scored

**Xenical\textsuperscript{®} versus Alli\textsuperscript{™}**: Orlistat is a reversible lipase inhibitor that acts by reducing the absorption of dietary fats in the lumen of the small intestine.\textsuperscript{15} It is commercially available as Xenical\textsuperscript{®}, a prescription-only formulation, and as Alli\textsuperscript{™}, an over-the-counter product, and is currently the only long-term drug treatment option for weight loss management. Some important differences between Xenical\textsuperscript{®} and Alli\textsuperscript{™} are summarized in Table 3. Orlistat may impair the absorption of fat soluble vitamins (e.g., A, D, E, K); to prevent fat soluble vitamin deficiency, a multiple vitamin supplement should be taken once a day at least 2 hours before or after orlistat administration. Due to orlistat’s interference with vitamin K absorption, patients on concurrent warfarin therapy should be closely monitored. Orlistat is contraindicated in patients with malabsorption syndrome or cholestasis; its most common adverse reactions include gastrointestinal (GI) symptoms related to the malabsorption of fat such as oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation and fecal incontinence. Patients receiving orlistat therapy should be advised to follow a reduced low-fat diet to help prevent GI side effects. There have been several postmarketing safety concerns with orlistat. Last year the FDA required respective manufacturers of Xenical\textsuperscript{®} and Alli\textsuperscript{™} to include a warning about hepatotoxicity in their product labeling.\textsuperscript{18} Furthermore, a recent study has linked orlistat use with acute kidney injury.\textsuperscript{19}
<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>FDA Status</th>
<th>FDA-Approved Indications</th>
<th>BMI Requirement</th>
<th>Dose*</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenical®</td>
<td>Roche</td>
<td>Rx-only</td>
<td>Obesity management: weight loss and management; prevention of weight regain</td>
<td>BMI ≥ 30 kg/m² or ≥ 27 kg/m² with risk factors (e.g., hypertension, diabetes, dyslipidemia)</td>
<td>120 mg three times a day with each main meal containing fat; may be taken during or up to 1 hour after each meal</td>
<td>Cyclosporine should be taken at least 2 hours before or after Xenical®. Levothyroxine should be taken at least 4 hours apart from Xenical®. Patients on warfarin therapy should be closely monitored.</td>
</tr>
<tr>
<td>Alli™</td>
<td>GlaxoSmithKline</td>
<td>OTC</td>
<td>Weight loss in overweight adults when used with a reduced calorie/low fat diet</td>
<td>BMI = 25 to 29 kg/m²</td>
<td>60 mg with each meal that containing fat up to three times a day</td>
<td>Not recommended for use with cyclosporine. Consult physician if using warfarin, medications for diabetes or thyroid disorder.</td>
</tr>
</tbody>
</table>

FDA=Food and Drug Administration  
Rx=Prescription  
OTC=Over-the-Counter  
BMI=Body Mass Index  
*Diet should not contain >30% of calories from fat; if meal is skipped or does not contain fat, dose should be omitted.
Weight Loss Medications Withdrawn from the Market: Safety data demonstrating an increased incidence of drug-induced cardiovascular events have prompted the removal of certain weight-loss agents from the market. Fenfluramine/phentermine (Fen-Phen), which was widely used as combination weight loss drug in the 1990’s, was discontinued in 1997 after it found to cause pulmonary hypertension and cardiac valvular disease. However phentermine, used as monotherapy, was deemed to be safe and effective in the treatment of weight loss and remained on the market.

In 2010, the Sibutramine Cardiovascular OUTcomes (SCOUT) trial evaluated the long-term effects of sibutramine also known as Meridia® on patients with preexisting cardiovascular disease and/or type 2 diabetes mellitus. This study reported a statistically significant increase in myocardial infarction (MI) and stroke in the sibutramine group compared to the placebo arm (4.2% and 2.6% in the sibutramine group and 3.2% and 1.9% in the placebo group, respectively; p=0.02 for MI, and p=0.03 for stroke). Consequently, sibutramine was voluntarily withdrawn from the U.S. market since FDA experts believed that the drug’s cardiovascular risk far outweighed any beneficial effect on weight management.

Investigational Weight Loss Agents: Last year several new drug applications (NDAs) for antiobesity medications were submitted to the FDA, however to date, none have currently received approval. Qnexa®, a combination agent which contains topiramate, an antiepileptic drug found to cause weight loss, and phentermine was reviewed in October 2010. A Phase III clinical trial demonstrated that the percentage of patients in the two Qnexa® treatment groups who achieved ≥5% weight loss at 1 year was significantly greater than those taking placebo (p<0.0001). Common drug-related side effects included dry mouth, paresthesias, constipation, altered taste, and insomnia. The FDA did not approve Qnexa® due to concerns about psychiatric/cognitive abnormalities, cardiovascular side effects, and topiramate-related birth defects.

Lorcaserin (Lorquess®) is an investigational antiobesity medication which suppresses appetite by stimulating the 5-HT²C receptors in the hypothalamus. Although a clinical study demonstrated that more patients in the lorcaserin treatment group achieved ≥10% weight loss in 1 year than those in the placebo group (p<0.001), the FDA denied approval since the drug was linked to tumor formation in rats. Vivus, the manufacturer of Qnexa®, and Arena Pharmaceutical, the manufacturer of Lorquess®, are still in discussions with the FDA to determine requirements for possible NDA resubmission. Contrave®, a combination drug containing naltrexone and bupropion, was thought to be another promising weight loss agent. Results of the Contrave Obesity Research I study reported that patients who received naltrexone 32 mg plus bupropion 360 mg had a statistically significant mean percent reduction in weight loss compared to those receiving placebo (p<0.0001); however, patients in the treatment group experienced a transient increase in blood pressure. In February 2011, the FDA announced that a large study evaluating cardiovascular outcomes must be conducted before the drug will be considered for approval; Orexigen Therapeutics, the manufacturer of Contrave®, will need to decide whether it is fiscally feasible to conduct this study and resubmit an updated NDA. The proposed mechanism of action, common side effects, and FDA concerns associated with these investigational agents are summarized in Table 4.

Table 4: Investigational Weight Loss Agents

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Mechanism of Action</th>
<th>Common Side Effects</th>
<th>FDA Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qnexa®</td>
<td>phentermine/topiramate</td>
<td>CNS stimulation/ enhance GABA activity</td>
<td>Paresthesias, altered taste, urinary frequency, constipation, insomnia</td>
<td>Psychiatric/ cognitive effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Topiramate-induced birth defects</td>
</tr>
<tr>
<td>Lorquess®</td>
<td>lorcaserin</td>
<td>Stimulation of 5-HT²C receptors in hypothalamus</td>
<td>Headache, dizziness</td>
<td>Potential for tumor formation</td>
</tr>
<tr>
<td>Contrave®</td>
<td>naltrexone/bupropion</td>
<td>Stimulation of the melanocortin pathway in hypothalamus</td>
<td>Headache, dizziness, constipation, vomiting, dry mouth</td>
<td>Cardiovascular risks</td>
</tr>
</tbody>
</table>

FDA=Food and Drug Administration
CNS= Central Nervous System
GABA= Gamma Amino Butyric Acid
5-HT=Serotonin
Conclusion: Obesity is a serious condition that increases the incidence of diabetes, hypertension, and cardiovascular disease. Weight loss, exercise, and behavior modification are the mainstays of therapy for obese patients. If lifestyle changes do not produce optimal results, weight loss medications or bariatric surgery may be considered for certain high risk patients. Pharmacotherapy is currently limited to SAs (e.g., diethylpropion, benzphetamine, phentermine) or orlistat (e.g., Xenical®, Alli™). Both of these therapeutic choices are associated with certain undesirable side effects. However, for now these agents remain the only pharmaceutical options for weight loss management since FDA-approval of newer drug entities has been stalled due to numerous safety concerns.

References:

8. Leonard M. Medications used in the management of obesity. Presented at the Cleveland Clinic Department of Pharmacy Noon Conference October 2010.