Neurobiological Understanding of Obesity: New Treatment Guidelines and Patient-Centered Approach

Learning Objectives
After participating in this educational activity, participants should be able to:

1. Screen for risk factors of obesity and diagnose obesity as a disease early in its evolution
2. Prescribe pharmacological intervention for obesity based on the neurobiology and pathophysiology of the disease following the National Heart, Lung and Blood Institute (NHLBI) guidelines
3. Describe the safety and efficacy studies of various agents and create awareness of post marketing and long term pharmacovigilance studies to assess long term risks
4. Focus on obesity as disease and provide communication strategies to build ongoing collaborative relationships with obese patients
Adult Obesity: Overview of the Current Environment in the US

Obesity is a major public health issue in this country, affecting over 78 million adult Americans. Adult overweight and obesity rates have risen dramatically within the past twenty years. Approximately 69% of adults in the United States (US) are either overweight (BMI≥25) or obese, and about 35% are obese (BMI≥30).[1]

Obesity increases the risk of many serious comorbid conditions, and is also associated with increased risk of all-cause and cardiovascular disease (CVD) mortality.

Figure 1. Medical Complications of Obesity[2]

The medical care costs of obesity in the US are staggering. In 2008, these costs totaled about $147 billion. Compared with normal-weight individuals, obese patients incur 46% higher inpatient costs, 27% more physician visits and outpatient costs, and 80% higher spending on prescription drugs.[3]

The Etiology of Obesity
The causes of obesity are multifactorial and vary from patient to patient, so the treatment strategies must be both comprehensive and individualized to meet the needs of the patient.

Genetics confer the potential for obesity. A parental history of obesity is a significant risk factor, especially if both parents are obese. However Environmental Factors determine whether and to what extent that genetic potential is realized.

Environmental Factors that Contribute to Weight Gain

- Life Events (aging, pregnancy, menopause)
- Medications (steroids, insulin, sulfonylureas, TZDs, antidepressants, atypical antipsychotics, etc.)
- Medical Conditions (hypothyroidism, Cushing’s syndrome, polycystic ovary syndrome, others)
- Smoking Cessation (stopping smoking still leads to significantly reduced CVD risk, all-cause mortality)
- Sleep Deprivation

Neurobiology of Obesity

By the time a body reaches obese proportions, its entire physiology has gone haywire. No longer is food intake intended to satisfy nutritional needs, “homeostatic feeding.” Instead, feeding has transformed into “non-homeostatic,” meaning that an individual eats for pleasure and tends to over-consume palatable food. Not only is there an exaggerated consumption of palatable food, there is a loss of control over food intake. Biologically, overeating may be a form of addiction.[4]

Not too long ago, hunger motivated our ancestors to eat. The selection of food was limited, difficult to obtain, or too costly. Satiety was the ultimate goal of eating. Today, however, the diversity, availability, and affordability of food sidelined the internal signal of “enough,” and was replaced with the rewards of flavor, texture, and all-you-can-eat buffets.[5]

Molecularly, obesity encompasses insulin and leptin resistance. In fact, leptin resistance tends to enhance craving for palatable food. Dopamine too is central to becoming motivated to overeat. These neuropeptides interfere with homeostatic feeding.

The melanocortin system is a crucial neuropeptidergic system that modulates feeding behavior. In addition, there is an inter-relationship between neurons in the arcuate nucleus that regulates energy homeostasis and reward circuitry.[6]

These findings are important to discuss with obese patients, who usually feel at a loss of what to do. They need to know that their condition has become a biological phenomenon that can be treated with a combination of pharmacology and changes in lifestyle habits.[7]

Identifying Patients Who Would Benefit from Weight Loss

One major barrier to combating this epidemic is that obesity often goes undiagnosed. Obesity has recently been recognized by major medical organizations as a disease in itself, and not just a risk factor. Combating the obesity epidemic requires comprehensive management and
prevention strategies. However, it cannot be treated if it is not diagnosed. A diagnosis of obesity in the Primary Care Provider’s (PCP’s) office is the strongest predictor that an obesity management plan will be formulated. Recognizing the importance of PCPs in obesity management, the US Preventive Services Task Force (USPSTF) recommends that clinicians screen all adult patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults (B Recommendation).[8] They define a high-intensity intervention as more than 1 person-to-person (individual or group) session per month for at least the first three months of the intervention.

The Centers for Medicare & Medicaid Services (CMS) covers intensive behavioral therapy for obesity. Intensive behavioral therapy must include:[9]

- Screening for obesity in adults using measurement of body mass index (BMI)
- Dietary (nutritional) assessment
- Intensive behavioral counseling and behavioral therapy to promote sustained weight loss through high intensity interventions on diet and exercise

CMS will cover counseling provided by a qualified primary care physician or other primary care practitioner and in a primary care setting as follows:

- One face-to-face visit every week for the first month
- One face-to-face visit every other week for months 2-6
- One face-to-face visit every month for months 7-12, if the beneficiary lost 3 kg in the first six months

For beneficiaries who do not achieve a weight loss of at least 3 kg during the first six months of intensive therapy, a reassessment of their readiness to change and BMI is appropriate after an additional six month period.

There are clear and specific diagnostic criteria for overweight and obesity based on body mass index (BMI – weight in kg/height in meters):[10]

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
</tr>
<tr>
<td>Class I Obese</td>
<td>30.0 - 34.9</td>
</tr>
<tr>
<td>Class II Obese</td>
<td>35.0 - 39.9</td>
</tr>
<tr>
<td>Class III Obese</td>
<td>≥ 40 (extreme obesity)</td>
</tr>
</tbody>
</table>

Recent increases in the use of electronic medical records and meaningful use requirements for documentation of BMI have made it much easier for clinicians to identify patients who are overweight and obese. However, BMI is not the only weight-related risk factor associated with increased morbidity and mortality. A waist circumference of >40 inches (>102 cm) in men and >35 inches (>88 cm) in women is strongly associated with an increased risk of diabetes, CVD and all-cause mortality, independent of BMI.

In 2013, the American Heart Association (AHA) Task Force on Practice Guidelines, The American College of Cardiology (ACC), and The Obesity Society (TOS) published their Guidelines for the Management of Overweight and Obese Adults.[11] These guidelines are designed to assist PCPs
with identifying appropriate patients for treatment, and providing their patients with evidence-based treatment approaches to help them lose weight, and then maintain their weight loss.

The 2013 AHA/ACC/TOS Guidelines recommend that PCPs:

- Measure height and weight and calculate BMI at annual visits or more frequently, depending on patient’s risk factors (i.e., hypertension, hyperlipidemia, hyperglycemia).
- Advise overweight and obese adults that the greater the BMI, the greater the risk of CVD, type 2 diabetes, and all-cause mortality.
- Assess and Treat Cardiovascular Risk Factors and Obesity-related Comorbidities
  - Risk assessment for CVD and diabetes in a person with overweight or Class I to III obesity includes history; physical examination; and clinical and laboratory assessments, including blood pressure (BP), fasting blood glucose, and fasting lipid panel.
  - A waist circumference measurement is recommended for individuals with BMI 25-34.9 kg/m² to provide additional information on risk. It is unnecessary to measure waist circumference in patients with BMI ≥35 kg/m² because the waist circumference will likely be elevated and will add no additional risk information.
  - Because obesity is associated with increased risk of hypertension, dyslipidemia, diabetes, and a host of other comorbidities, the clinician should assess for associated conditions. Intensive management of cardiovascular risk factors (hypertension, dyslipidemia, prediabetes, or diabetes) or other obesity-related medical conditions (e.g., sleep apnea) be instituted if they are found, regardless of weight loss efforts.

Diet and Lifestyle Modification Approaches

Patients should be prescribed a diet to achieve reduced caloric intake, considering the patient’s preferences and health status, as part of a comprehensive lifestyle intervention. This can be achieved by referring the patient to a nutrition professional for counseling.

When recommending a diet for weight loss it is important to understand that there is no ideal diet for weight loss and no superiority for any of the myriad diets reviewed.

The 2013 AHA/ACC/TOS Guidelines recommend that PCPs:

- Counsel overweight and obese adults with cardiovascular risk factors (hypertension, hyperlipidemia, hyperglycemia) that lifestyle changes that produce even modest, sustained weight loss of 3%-5% produce clinically meaningful health benefits, and greater weight losses produce greater benefits.
- Sustained weight loss of 3%-5% is likely to result in clinically meaningful reductions in triglycerides, blood glucose, hemoglobin A1c, and the risk of developing type 2 diabetes.
- Greater amounts of weight loss will reduce BP, improve LDL–C and HDL–C, and reduce
the need for medications to control BP, blood glucose, and lipids as well as further reduce triglycerides and blood glucose.

- Prescribe a diet to achieve reduced calorie intake for obese or overweight individuals who would benefit from weight loss, based on the patient’s preferences and health status, as part of a comprehensive lifestyle intervention. Any one of the following methods can be used to reduce food and calorie intake:
  - Refer to a nutrition professional for counseling (preferred)
  - Prescribe 1200–1500 kcal/day for women and 1500–1800 kcal/day for men (kilocalorie levels are usually adjusted for the individual’s body weight)
  - Prescribe a 500 kcal/day or 750 kcal/day energy deficit
  - Prescribe one of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake

### Lifestyle Intervention and Counseling

The 2013 AHA/ACC/TOS Guidelines recommend that PCPs:

- Advise overweight and obese individuals who would benefit from weight loss to participate for ≥6 months in a comprehensive lifestyle program that assists participants in adhering to a lower-calorie diet and in increasing physical activity through the use of behavioral strategies.

- Prescribe on-site, high-intensity (i.e., ≥14 sessions in 6 months) comprehensive weight loss interventions provided in individual or group sessions by a trained interventionist.

- Electronically delivered weight loss programs (including by telephone) that include personalized feedback from a trained interventionist can be prescribed for weight loss, but may result in smaller weight loss than face-to-face interventions.

- Some commercial-based programs that provide a comprehensive lifestyle intervention can be prescribed as an option for weight loss, provided there is peer-reviewed published evidence of their safety and efficacy.

- Use a very-low-calorie diet (defined as <800 kcal/day) only in limited circumstances and only when provided by trained practitioners in a medical care setting where medical monitoring and high-intensity lifestyle intervention can be provided. Medical supervision is required because of the rapid rate of weight loss and potential for health complications.

- Advise overweight and obese individuals who have lost weight to participate long-term (≥1 year) in a comprehensive weight loss maintenance program.

- For weight loss maintenance, prescribe face-to-face or telephone-delivered weight loss maintenance programs that provide regular contact (monthly or more frequently) with a trained interventionist who helps participants engage in high levels of physical activity (i.e., 200–300 minutes/week), monitor body weight regularly (i.e., weekly or more frequently), and consume a reduced-calorie diet (needed to maintain lower body weight).
**Exercise Recommendations**

The US Department of Health and Human Services’ (HHS) 2008 *Physical Activity Guidelines for Americans* recommends that for general health all adults obtain at least 150 minutes a week of moderate intensity physical activity or equivalent, and perform resistance training of moderate or high intensity on 2 or more days a week.[12] However, to achieve weight loss and maintenance the guidelines recommend:

- 150 to 250 minutes per week of moderate intensity physical activity. This serves as good foundation for diet and exercise based weight loss programs.
- Obtaining 250 minutes or more per week of moderate intensity physical activity plays an important role in maintaining weight loss.

**Utilizing Pharmacologic Agents for Weight Loss**

Obesity is a complex chronic disease that requires multiple treatment options.

The 2013 AHA/ACC/TOS Guidelines recommend that for individuals with BMI \( \geq 30 \text{ kg/m}^2 \) or BMI \( \geq 27 \text{ kg/m}^2 \) with \( \geq 1 \) obesity-associated comorbid condition(s) who are motivated to lose weight, pharmacotherapy can be considered as an adjunct to comprehensive lifestyle intervention to help achieve targeted weight loss and health goals.

- Medications should be FDA approved, and clinicians should be knowledgeable about the product label.
- The provider should weigh the potential risks of the medication being considered against the potential benefits of successful weight loss for the individual patient.
- The rationale for use of medications is to help patients:
  - Better adhere to a lower-calorie diet more consistently
  - Achieve clinically significant sufficient weight loss and related health improvements when combined with increased physical activity
  - Sustain weight loss

Weight loss medications are not effective on their own. They should be used as an adjunct to lifestyle counseling.

There are currently five FDA-approved pharmacologic agents for management of obesity, but only two were available prior to 2012. All five agents are Pregnancy Category X.
Table 1. FDA Approved Obesity Pharmacologic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Common Adverse Effects</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Central non-adrenergic (Schedule IV agent)</td>
<td>• Restlessness</td>
<td>15 mg - 37.5 mg PO QD with breakfast or 1-2 hours after breakfast</td>
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<tr>
<td></td>
<td></td>
<td>• Insomnia</td>
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<tr>
<td></td>
<td></td>
<td>• Increased pulse</td>
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<tr>
<td></td>
<td></td>
<td>• Increased BP</td>
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<tr>
<td>Orlistat</td>
<td>Peripheral Pancreatic lipase inhibitor, blocking absorption of dietary fat</td>
<td>• GI symptoms: - Steatorrhea</td>
<td>60-120 mg PO TID with each meal containing fat</td>
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<tr>
<td></td>
<td></td>
<td>- Flatus with discharge</td>
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<tr>
<td></td>
<td></td>
<td>- Fecal urgency</td>
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<td></td>
<td></td>
<td>- Fecal incontinence</td>
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<tr>
<td>Lorcaserin HCL</td>
<td>5-HT2C specific serotonin agonist, reducing food intake and increasing satiety</td>
<td>• Headache</td>
<td>10 mg PO BID, with or without food. d/c if &lt;5% weight loss by week 12</td>
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<tr>
<td></td>
<td></td>
<td>• URI</td>
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<tr>
<td></td>
<td></td>
<td>• Nasopharyngitis</td>
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<td></td>
<td></td>
<td>• Dizziness</td>
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<tr>
<td></td>
<td></td>
<td>• Nausea</td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Sympathomimetic anticonvulsant (GABA receptor modulation, carboxylic anhydrase inhibition, glutamate antagonism)</td>
<td>• Dry mouth</td>
<td>Initiate 3.75/23 mg dose QAM with or without food x 14 days, then titrate to 7.5/46 mg dose QAM. d/c or titrate if &lt;3% weight loss by week 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paraesthesia</td>
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<td></td>
<td></td>
<td>• Constipation</td>
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<td></td>
<td>• Dysgeusia</td>
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<tr>
<td></td>
<td></td>
<td>• Insomnia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Dizziness</td>
<td></td>
</tr>
<tr>
<td>Bupropion SR/ Naltrexone SR</td>
<td>Opioid receptor antagonist combined with a norepinephrine and dopamine receptor reuptake inhibitor</td>
<td>• Nausea</td>
<td>A total daily dosage of two, 8 mg/90 mg tablets twice daily (32 mg/360 mg) is reached at the start of week 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Constipation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Headache</td>
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<tr>
<td></td>
<td></td>
<td>• Vomiting</td>
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<td></td>
<td></td>
<td>• Dizziness</td>
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<tr>
<td></td>
<td></td>
<td>• Dry mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diarrhea</td>
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</tr>
</tbody>
</table>

Gastrointestinal (GI); Upper Respiratory Infection (URI)

**Older Agents**

**Phentermine**

Mechanism of Action
Phentermine is an anorectic sympathomimetic amine agent, which was first approved in 1959.\cite{13} It is approved as an appetite suppressant to help reduce weight in obese patients when used short-term and combined with a lifestyle program of exercise, diet, and behavioral modification. Phentermine works on the hypothalamus to stimulate the adrenal glands to release norepinephrine, reducing hunger. It is a Schedule II-IV controlled substance with a strict three-month prescribing limit.

**Efficacy**
The effectiveness of phentermine has been studied in a number of trials. All trials in which phentermine was used exclusively were 20 weeks or less in length. These studies show that use of this medication results in an average weight loss of 6.6 pounds.

**Side Effects/Contraindications**
The most common side effects of phentermine are dry mouth, restlessness, nervousness, agitation, tachycardia, elevated blood pressure, diarrhea, vomiting, and headache. It is contraindicated in patients with hyperthyroidism, glaucoma, peptic ulcer, prostatic hypertrophy, and epilepsy, cardiovascular disease, as well as patients on SSRIs, SNRIs, or TCAs.

**Dosage**
The dosage of phentermine varies by manufacture from 15 mg - 37.5 mg, usually administered once daily with breakfast or 1-2 hours after breakfast. For some patients half the dose two times a day may be more desirable. The dosage should be individualized to obtain an adequate response with the lowest effective dose.

**Orlistat**

**Mechanism of Action**
Orlistat is a peripheral pancreatic lipase inhibitor, blocking dietary fat absorption, thereby reducing caloric intake. It has been FDA-approved since 1999. It is not a controlled substance/scheduled agent.

**Efficacy**
Orlistat has been shown in various studies to cause significant, though modest weight loss. The average patient loses about 2–3 kg (4.4–6.6 lb) over a 12 month period, compared with placebo, when combined with a lifestyle modification program, including diet and exercise.\cite{14}

A large Randomized Control Trial (RCT) demonstrated orlistat’s ability to also reduce the incidence of diabetes by almost 40% in obese patients. Orlistat has also been shown to modestly reduce BP.

Orlistat has been shown to help reduce the incidence of type 2 diabetes in obese patients. The XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study was a 4-year, double-blind, randomized control trial of 3,305 patients evaluating orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients.\cite{15} Patients were randomized to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. Participants had a BMI ≥30 kg/m² and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were onset of type 2 diabetes and change in body weight. After 4 years’ treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (P = 0.0032). The preventive effect was explained by the difference in subjects with IGT. Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; P < 0.001) and similar between orlistat recipients with impaired (5.7 kg) or normal glucose tolerance (NGT) (5.8 kg) at baseline. Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes.
over 4 years and produced greater weight loss in a clinically representative obese population. Difference in diabetes incidence was detectable only in the IGT subgroup; weight loss was similar in subjects with IGT and or NGT.

**Side Effects/Contraindications**

Orlistat’s greatest limitation is its highly prevalent gastrointestinal side effects, including steatorrhea (oily, loose stools), fecal urgency, increased defecation, and fecal incontinence. These effects decrease with time, however.

**Dosage**

The recommended dose of orlistat is 120 mg orally three times a day with each main meal containing fat (during or up to 1 hour after the meal). The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over three main meals. If a meal is occasionally missed or contains no fat, the dose can be omitted. Because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition.

**Newer Agents**

**Lorcaserin**

**Mechanism of Action**

Lorcaserin is a 5-HT2c specific serotonin receptor agonist. It appears to stimulate these receptors on the hypothalamic proopiomelanocortin neurons, reducing food intake and increasing satiety, which then leads to weight loss. It has been FDA-approved since summer 2012.

**Efficacy**

In three clinical trials, lorcaserin was found to be efficacious for adjunctive therapy and maintenance of weight loss. When taken as directed, it causes a low to moderate incidence of adverse drug events compared with other weight-loss agents. Lorcaserin appears to be well tolerated in patients and the most common adverse events reported did not include serious complications.[16,17]

**Side Effects/Contraindications**

The most common adverse effects of lorcaserin included upper respiratory tract infection, headaches, dizziness, nasopharyngitis, and nausea. Lorcaserin has not been studied in patients taking antidepressants. The label advises use with extreme caution in patients taking SSRIs, SNRIs, MAOIs, and other serotonergic drugs.

Lorcaserin shows high selectivity for the 5-HT2C receptor subtype, with minimal activity at 5-HT2B or 5-HT2A receptor subtypes. It’s mechanism of action is similar to fenfluramine (various brand names) and dexfenfluramine, which were removed from the market due to reports of heart valve issues. However, lorcaserin is specific for the 2c serotonin receptor that is not found in the heart or heart valves. Echo studies have showed no increased incidence of FDA-defined cardiac valvulopathy. The FDA still requires a label warning about the potential risk of valvular heart disease because sample size from echo studies are too small to exclude the possibility.
**Dosage**
The recommended dose of lorcaserin is 10 mg administered orally twice daily. It 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, lorcaserin should be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

No dosing adjustments are required in patients with mild-to-moderate hepatic or renal impairment. However, it is not recommended to use lorcaserin in severe renal disease (creatinine clearance <30 mL per minute).

**Phentermine/ Topiramate ER (Extended-Release)**

**Mechanism of Action**
Phentermine/Topiramate ER (Qsymia) combines the appetite-suppressant effect of a sympathomimetic agent with an anticonvulsant. FDA-approved since summer 2012.

**Efficacy**
Both doses of phentermine plus topiramate, in combination with lifestyle intervention, resulted in significant weight loss and comorbid risk reduction. The weight loss was sustained for the duration of the 56-week trial.[18,19] In combination the drugs have shown greater weight reduction than either agent alone.

**Side Effects/Contraindications**
Side-effect profiles of topiramate and phentermine are already well established, and in CONQUER trial reflected what has been seen in clinical experience with these agents as monotherapy: dry mouth, paresthesias, constipation, insomnia, dizziness, and dysgeusia.

**Dosage**
Phentermine/Topiramate ER dosing needs to be titrated. It is taken once daily in the morning with or without food. It should not be taken in the evening due to the possibility of insomnia. The starting dose is 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg ER) daily for 14 days; after 14 days increase to the recommended dose of 7.5 mg/46 mg (phentermine 7.5 mg/topiramate 46 mg ER) once daily.

Weight loss should be evaluated after 12 weeks of treatment with the 7.5 mg/46 mg dose. If a patient has not lost at least 3% of baseline body weight, the medication should either be discontinued or the dose increased, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss at the 7.5 mg/46 mg dose. To escalate the dose: Increase to 11.25 mg/69 mg (phentermine 11.25 mg/topiramate 69 mg ER) daily for 14 days; followed by dosing 15 mg/92 mg (phentermine 15 mg/topiramate 92 mg ER) once daily.

Evaluate weight loss following dose escalation to 15 mg/92 mg after an additional 12 weeks of treatment. If a patient has not lost at least 5% of baseline body weight on that dose, the medication should be discontinued as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

- 3.75 mg/23 mg and 11.25 mg/69 mg dosages are for titration purposes only.
- Discontinue 15 mg/92 mg gradually by taking a dose every other day for at least 1 week.

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prior to stopping treatment altogether, due to the possibility of precipitating a seizure.

- Doses are lower than single agents (phentermine 15-30 mg for weight loss or topiramate <200 mg for migraine prophylaxis).

**Bupropion SR/Naltrexone SR (Slow-Release)**

**Mechanism of Action**
Bupropion SR/Naltrexone SR combination functions as an opioid receptor antagonist combined with a norepinephrine and dopamine receptor reuptake inhibitor. Bupropion has neuronal effects that lead to reduced energy intake and increased energy expenditure. Naltrexone was chosen as a complement to bupropion in order to block compensating mechanisms that attempt to prevent long-term, sustained weight loss. On September 9, 2014, Bupropion SR/Naltrexone SR was approved for the treatment of obesity following the completion of four pivotal trials.

**Efficacy**
In previous studies, the combination therapy helped patients to lose 5% or more of their body weight in 53% of cases, compared to 21% placebo over the 12-month trial duration. In the Contrave Obesity Research (COR) program, 34-48% of patients lost at least 10% of their baseline body weight after 56 weeks of therapy. Cholesterol levels and blood sugar control improvements were also observed in many patients.

**Side Effects/Contraindications**
The most common side effects include nausea, constipation, headache, vomiting, dizziness, trouble sleeping, dry mouth, and diarrhea. Suicidal thoughts or actions may also be observed.

**Dosage**
Extended release tablets: 8 mg naltrexone HCI/90 mg bupropion HCL are indicated for adults with BMI of >30 kg/m² or >27 kg/m². Tablets should be taken in the morning and the evening. A total daily dosage of two, 8 mg/90 mg tablets twice daily (32 mg/360 mg) is reached at the start of week 4.

**Medications Awaiting Approval (Possibly late 2014/Early 2015)**

**Liraglutide**
This GLP-1 receptor agonist was approved in 2010 for treatment of type 2 diabetes (1.8 mg/day). Its anorectic effect is mediated both by the activation of GLP-1 receptor expressed on vagal afferents and by the GLP-1R activation in CNS. The GLP-1 mode of action delays gastric emptying and induces satiety, which is probably related to the combined effect of GLP-1 on the gastrointestinal tract and the brain. Liraglutide affects visceral fat adiposity, appetite, food preference, and cardiovascular biomarkers in patients with type 2 diabetes. A new drug application was submitted to the FDA on December 20, 2013, for approval for use in the treatment of obesity. On September 11, 2014, the FDA Advisory Committee voted to support approval for the injectable liraglutide. Liraglutide will carry much from its diabetes label in terms of precautions and warnings. Preliminary data support that FDA efficacy criteria have been met.

**Cetilistat**

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Cetilistat acts in the same way as orlistat by inhibiting pancreatic lipase. Without this enzyme, triglycerides from the diet are prevented from being hydrolyzed into absorbable free fatty acids and are excreted undigested. In human trials, cetilistat was shown to produce similar weight loss to orlistat, but also produced similar side effects such as oily, loose stools, fecal incontinence, frequent bowel movements, and flatulence. It is likely that the same precautions would apply in that absorption of fat-soluble vitamins and other fat-soluble nutrients may be inhibited, requiring vitamin supplements to be used to avoid deficiencies. Cetilistat has completed Phase 1 and 2 trials in the West and is currently in Phase 3 trials in Japan. A published Phase 2 trial found cetilistat significantly reduced weight and was better tolerated than orlistat.[20]

**Bariatric Surgical Treatment for Obesity**

Selecting Patients for Bariatric Surgical Treatment for Obesity

- Advise adults with a BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity-related comorbid conditions who are motivated to lose weight and who have not responded to behavioral treatment with or without pharmacotherapy with sufficient weight loss to achieve targeted health outcome goals that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation.

- For individuals with a BMI < 35 kg/m², there is insufficient evidence to recommend for or against undergoing bariatric surgical procedures.

- Advise patients that choice of a specific bariatric surgical procedure may be affected by patient factors, including age, severity of obesity/BMI, obesity-related comorbid conditions, other operative risk factors, risk of short- and long-term complications, behavioral and psychosocial factors, and patient tolerance for risk, as well as provider factors (surgeon and facility).

**Putting it All Together**

1. Diagnose: Obtain BMI on all patients. Waist Circumference if BMI 25-34.
2. Communicate: Address weight loss with all patients BMI > 30 or BMI > 27 with at least one comorbid risk factor.
3. Manage: Consider prescribing medications with a lifestyle intervention early for patients with BMI > 30 or BMI > 27 with at least one comorbid risk factor.
4. Reassess: Have patient follow up for regular individualized counseling.
5. Refer: Consider bariatric surgery referral for patients with BMI > 40 or BMI > 35 with at least one comorbid risk factor.