A Review of New Guidelines and Treatment Options for Obesity

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Upon successful completion of this article, the pharmacist should be able to:
1. Explain the key pharmacologic considerations for each Food and Drug Administration-approved chronic obesity medications.
2. Describe recent guidelines on pharmacologic and nonpharmacologic management of obesity.
3. Recommend clinically appropriate obesity medications on a patient by patient basis.

Upon successful completion of this article, the pharmacy technician should be able to:
1. List the prescription drugs that are approved by FDA for treatment of chronic obesity.
2. Describe recent guidelines on pharmacologic and nonpharmacologic management of obesity.
3. Choose an appropriate course of action if a patient taking a prescription medication for the treatment of obesity appears to be experiencing an adverse event.

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INTRODUCTION

Obesity is a common diagnosis in the United States and affects more than one-third of adults. As we learn more about obesity, there is an increasing interest in developing programs and treatments to both help prevent its development and lessen its negative effects.

BMI Calculation

\[
\text{BMI kg/m}^2 = \frac{\text{Weight (kilograms)}}{\text{Height (meters)}^2}
\]

Obesity is defined by the World Health Organization as “abnormal or excessive fat accumulation that may impair health.” Adults are commonly classified as being obese based on their body mass index (BMI). A BMI of greater than or equal to 25 kg/m² is considered overweight and a BMI of greater than or equal to 30 kg/m² is considered obese. As a point of reference, someone who is 5 feet 6 inches tall would be obese if they are 186 pounds or greater and someone who is 6 feet tall would be obese if they are 221 pounds or more.

Obesity is described as a national public health threat and is directly tied with an increased risk of morbidity and mortality. Obesity causes cardiovascular morbidity as well as morbidity from the respiratory system, some cancers, and other diseases as described in Table 1. The broad range of organ systems affected by these morbidities leads to increased health care expenditures treating acute illness and trying to lower long-term risk and symptoms. When compared to non-obese counterparts, obese patients experience 46 percent greater inpatient costs and 80 percent greater costs on prescription medications.

Table 1: Obesity Increases the Risk of the Following Disease States

- Hypertension
- Dyslipidemia
- Type 2 diabetes
- Coronary heart disease
- Stroke
- Gallbladder disease
- Osteoarthritis
- Sleep apnea and other respiratory diseases
- Certain cancers

*Adapted from the American Heart Association, American College of Cardiology, and the Obesity Society guidelines

OBESITY AS AN “ESSENTIAL HEALTH BENEFIT” WITHIN THE AFFORDABLE CARE ACT

Preventive care is gaining traction with payers, providers and patients in United States health care and this is likely in part influenced by the Affordable Care Act. Certain preventative services are outlined that need to be a part of health plans available on the individual market or for small groups as a result of the ACA. One of the services payers are required to cover is preventative care and chronic disease management. Each state defines how the essential health benefits will be covered, which results in specific services included varying from state to state. Recent analysis found that services with respect to obesity treatment vary greatly at the state level; 23 states cover bariatric surgery, 12 states include nutrition counseling, and only three states include weight loss programs as essential health benefits. However, treatment and prevention of obesity is a growing area, and so it is likely that more services for obesity will be covered in the future.

NONPHARMACOLOGIC TREATMENT OF OBESITY

The American Heart Association, American College of Cardiology, and the Obesity Society (AHA/ACC/TOS) published “2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults” (http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437739.71477.ee) regarding management of obesity. The full text of this guideline is available online from Circulation, the journal of the American Heart Association. This guideline covers topics surrounding obesity that do not relate to medications and certain key concepts are summarized here.

Identification

The first step to treatment is to identify patients who could benefit from weight loss. Patients who are either obese or overweight with comorbidities related to obesity or certain cardiovascular risks (such as prediabetes or waist circumference greater than 40 inches for men and 35 inches for non-pregnant women) are candidates for weight loss. Both BMI and waist circumference should be monitored and documented at least annually. Patients who are overweight or obese should be informed that as their BMI or waist circumference increases, their risk for diabetes, cardiovascular disease, and all-cause mortality becomes greater.

Communication of Benefits

The concept of weight loss is often overwhelming for many patients and this can be compounded by the daunting task of losing enough weight to achieve a normal weight (BMI 18.5 - 25 kg/m²). However, it is important to note that benefits can be obtained without reaching a normal weight. For instance, a sustained weight loss of only 3-5 percent can lead to important clinical benefits such as improved triglycerides and decreased risk of developing diabetes. That obese, 6-foot tall patient weighing 221 pounds referenced earlier in the article could see clinical benefit from losing 6-8 pounds, whereas it would require losing 37 pounds to have a healthy
BMI. Weight loss beyond 5 percent can lead to decreased need for medications to treat blood pressure and diabetes. An overall goal of 5-10 percent weight loss within six months is recommended through the AHA/ACC/TOS guideline.

Recommendations for Diets
The AHA/ACC/TOS guideline focuses on prescribing several different types of diets and three options are outlined: 1,200-1,500 kcal/day diet for women, or a 1,500-1,800 kcal/day diet for men; a diet that is 500-750 kcal/day less than the patient’s usual diet; or a diet that restricts certain food types and is evidenced-based. The guideline lists more than a dozen diets that have high strength of evidence for achieving weight loss.

Recommendations for Lifestyle Changes
Patients who would benefit from weight loss should be enrolled in a “comprehensive lifestyle program.” This sort of program is defined as one that provides at least 14 sessions over the course of six months and is administered by a professional trained for this work. It includes prescriptions for dieting, exercise, and also behavioral techniques to help patients adhere to these changes.

Surgical Treatment for Obesity
Patients are indicated for bariatric surgery if they are committed to losing weight, have failed lifestyle changes, and have a BMI greater than or equal to 40 kg/m2, or greater than or equal to 35 kg/m2 with certain comorbidities.

Medication Monitoring
When patients lose weight, their requirements for medications for blood pressure, diabetes, and other conditions related to obesity generally decrease. It is important for the clinician to monitor these medications closely and make adjustments as appropriate.

MEDICATIONS THAT LEAD TO WEIGHT GAIN
Many different medications can lead to weight gain and it is important for pharmacists to have an understanding of these medications in order to advise patients.

Medications Used to Treat Diabetes
Diabetes is a common comorbidity with obesity and several medications used to treat diabetes lead to weight gain. Medications such as insulin and sulfonylureas (such as a glyburide and glipizide) often lead to weight gain because their mechanism of action results in increased cellular uptake of glucose.

Experts suggest preferential use of diabetes medications that lead to weight loss. These medications include metformin, glucagon-like-peptide-1 (GLP-1) agonists (such as albiglutide, exenatide, and liraglutide), or sodium-glucose-linked transporter 2 (SGLT-2) inhibitors (such as canagliflozin, dapagliflozin, and empagliflozin). In an obese patient, the second two classes of medications should be added to metformin, which is still considered the first-line therapy for diabetes. For patients who need insulin, it is recommended that metformin, pramlintide, or GLP-1 agonists are also used to combat the weight-gain effects of insulin. Further, it is recommended that basal insulin be used preferentially over a mixed basal-bolus regimen. There are clearly many considerations surrounding the best medication regimens for concomitant diabetes and obesity, and key points to remember are that metformin remains first line and that diabetes medications that lead to weight loss are generally preferred as a first line addition to metformin, especially in cases where insulin is used.

Medications Used to Treat Depression
Depression is also a concomitant diagnosis to patients with diabetes and other chronic diseases, and medications used for depression have differing effects on weight. Antidepressants that are commonly associated with weight gain include tricyclic antidepressants (such as amitriptyline and nortriptyline) and mirtazapine. Bupropion can be considered as an antidepressant in an obese patient since it is the antidepressant often associated with weight loss.

Medications Used to Treat Schizophrenia
Schizophrenia medications can lead to changes in appetite that lead to weight gain. The side effects profile of atypical antipsychotics means they are preferred for many patients, but they often lead to weight gain. Clozapine, olanzapine, quetiapine, and risperidone are all associated with weight gain. Ziprasidone is commonly found to cause significantly less weight gain when compared with other atypical antipsychotics. The Endocrine Society recommends “using weight neutral antipsychotics when clinically indicated rather than those that cause weight gain, and the use of a shared decision making…”

Medications to Treat Epilepsy
Antiepileptic medications can lead to either weight gain or weight loss. For example, gabapentin, pregabalin, carbamazepine, and valproate have been found to cause weight gain, whereas topiramate and zonisamide may lead to weight loss. Similar to recommendations for antipsychotic and antipsychotic agents, the Endocrine Society recommends employing a shared-decision model when choosing the most appropriate antiepileptic with a patient.

Other medications to consider when assessing an obese patient include depot-medroxyprogesterone and corticosteroids. Studies evaluating weight gain and use of contracep-
tives report greater weight gain with depot-medroxyprogesterone than oral contraceptives, and little or no difference between women taking oral contraceptives and the control group. The other issue to consider is the estrogen dose in oral contraceptives. There is data that oral contraceptives with lower doses of estrogen may not be as effective in obese women as compared to non-obese women; however, it should be noted that often times the benefit outweighs the risk. If oral contraceptives containing estrogen are prescribed for obese women. Intrauterine devices are another option for effective contraception in women of normal and obese weight. When utilizing these medications in an obese patient for benefits other than contraception, other options for contraception (if desired), such as barrier methods, should be recommended. Corticosteroids may cause weight gain and may raise blood glucose, so consider other options for inflammation such as nonsteroidal anti-inflammatory drugs, if appropriate.

BRIEF HISTORY OF OBESITY MEDICATIONS
When considering the current medications approved by the FDA, an understanding of the history of obesity medications is important. Several medications have been removed from the market due to adverse cardiovascular side effects. This has undoubtedly led to increased hesitancy among prescribers when considering newly approved products.

Fenfluramine was approved in 1973 and increased satiety by increasing levels of 5-hydroxytryptamine (5-HT, serotonin). Several decades later, in 1996, the dexfenfluramine enantiomer was approved because it was thought to lead to fewer adverse effects. Due to cardiovascular adverse effects, both fenfluramine and dexfenfluramine were withdrawn from the market in 1997.

In the same year that fenfluramine and dexfenfluramine were withdrawn from the market, sibutramine was approved for treatment of obesity. Sibutramine works by inhibiting the reuptake of norepinephrine and serotonin. After cardiovascular adverse effects were reported, the SCOUT trial was initiated to further investigate cardiovascular effects of sibutramine. The composite outcome of non-fatal myocardial infarction (MI), nonfatal stroke, and resuscitation after cardiac arrest or CV death as well as the incidence of non-fatal MIs and non-fatal stroke were all found to be elevated when compared to placebo. The FDA requested the withdrawal of sibutramine from the market in 2010 after the results of this study were published. When sibutramine was withdrawn, the only remaining FDA-approved product for chronic management of obesity was orlistat.

Given the history of obesity medications leading to adverse cardiovascular side effects, many clinicians are more cautious in prescribing these medications. A discussion of the current approved medications for obesity is outlined below.

GENERAL RECOMMENDATIONS ABOUT MEDICATIONS RECENTLY APPROVED FOR OBESITY
Since 2012, four medications have been approved for the chronic treatment of obesity. Table 2 outlines all five FDA-approved medications for chronic treatment of obesity. There are some commonalities among all of the approved obesity medications. The indication is nearly identical for each of the medications and can be paraphrased as: weight loss & management in combination with low-calorie diet for adults with initial BMI ≥ 30 kg/m², or BMI ≥ 27 kg/m² with other weight-related comorbidities such as diabetes, hypertension, or dyslipidemia. The indications for some of the medications also include recommendations for an increase in physical activity. Providers should stress to patients the importance of combining both diet and exercise interventions with these medications. The practitioner should be aware that the clinical trials which led to approval for these medications included robust programs to assist participants in behavioral changes. If obesity medications are taken without the addition of behavioral changes, it is likely the weight loss that the patient achieves will be significantly less than what was demonstrated in the clinical trials.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Year of FDA Approval</th>
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</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical (prescription)</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td>Alli (over the counter)</td>
<td>2007</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
<td>2012</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>Qsymia</td>
<td>2012</td>
</tr>
<tr>
<td>Naltrexone/bupropion ER</td>
<td>Contrave</td>
<td>2014</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>2014</td>
</tr>
</tbody>
</table>
Pregnancy is a contraindication that is consistent across all of the medications for chronic treatment of obesity because of risk for fetal harm.

With the exception of orlistat, all of the medications for chronic treatment of obesity were approved with guidance from the manufacturer for discontinuation if predetermined efficacy measures are not achieved. The recommendations are outlined in Table 3. Although orlistat does not have product labeling that discusses discontinuation, it is reasonable to discuss a general plan with a patient of re-evaluating the use of orlistat at 12 weeks if weight loss is less than 5 percent.

**Table 3: Recommendations Within Package Labeling for Discontinuation of Chronic Obesity Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Discontinuation Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>None listed</td>
</tr>
<tr>
<td>Lorcaserin and Naltrexone/Bupropion ER</td>
<td>Discontinue at 12 weeks if weight loss is &lt;5%</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>At 12 weeks of treatment on the 7.5 mg/46 mg dose if weight loss is &lt;3%, consider stopping or increasing the dose. If the 15 mg/92 mg dose is used, discontinue after 12 weeks of this highest dosage if weight loss is &lt;5%.</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Discontinue at 16 weeks if weight loss is &lt;4%</td>
</tr>
</tbody>
</table>

Certain fat-soluble vitamins have demonstrated decreased absorption in patients taking orlistat. This occurs because orlistat inhibits the lipase that breaks down fat-soluble vitamins into absorbable components. Multivitamins have been shown to reverse the abnormal vitamin concentrations that were identified in clinical trials. The manufacturer of orlistat recommends administration of a multivitamin at least two hours before or after a dose of orlistat.

Orlistat has several known drug interactions—which are most often related to orlistat’s effect on decreasing absorption of other medications. Both the concentrations of levothyroxine and cyclosporine were decreased when administered with orlistat. It is recommended to separate doses of orlistat from cyclosporine by three hours and from levothyroxine by four hours. Concentrations of warfarin and antiepileptic medications may also be affected, and patients taking these medications should be monitored more closely if orlistat is initiated. Additionally, amiodarone may be affected, and due to the potential for sub-therapeutic levels, patients should be monitored.

Dosing of orlistat occurs in conjunction with meals. The prescription strength dose is 120 mg and the over-the-counter dose is 60 mg and is taken up to three times daily with each meal. Patients should be instructed to take orlistat at the same time as—or up to one hour after—their meals. Patients should only take orlistat with meals and should skip a dose if they are skipping a meal. Additionally, if a meal is eaten that does not contain fat, orlistat can be skipped.

**Lorcaserin (Belviq)**
Lorcaserin activates the 5-HT2c receptors subtype. This mechanism is similar to that of fenfluramine in that it...
increases serotonin levels, but the molecule is more selective. Because lorcaserin is selective for the 2C receptor subtype, it has not caused the adverse cardiac effects fenfluramine does. It is thought that activation of receptor subtypes other than the 2C subtype is what led to fenfluramine’s adverse cardiac effects.

Due to lorcaserin’s serotonergic effect, there are certain drug-drug interactions and side effects to monitor. (See Table 4.) Perhaps the most clear drug-drug interaction is the possibility of serotonin syndrome when lorcaserin is used concomitantly with other serotonin modulating medications. This includes medications that are traditionally known to increase serotonin levels such as selective serotonin reuptake inhibitors (SSRI) and selective noradrenaline reuptake inhibitors (SNRI), but also includes medications such as dextromethorphan, monoamine oxidase inhibitors (MAOI), lithium, triptans, and tramadol, as well as the herbal preparation St. John’s Wort. Additionally, lorcaserin is a CYP2D6 inhibitor and as a result, may increase the concentration of medications that are metabolized by CYP2D6, which includes many medications that modulate serotonin (such as fluoxetine, paroxetine, and venlafaxine). The combination of lorcaserin’s own action on serotonin with the potential for increased concentration of other serotonin modulating medications can put patients at greater risk for serotonin syndrome. Serotonin syndrome is often characterized by mental status changes, tachycardia, variable blood pressures, and/or neuromuscular abnormalities. Counsel patients taking these medications to immediately report these symptoms.

Among the available medications for chronic obesity, lorcaserin is well tolerated. Side effects that occurred in more than 10 percent of patients include upper respiratory tract infections, nasopharyngitis, and headache. Caution should be taken when lorcaserin is used in patients with diabetes as hypoglycemia is more frequent.

Lorcaserin is dosed as a 10 mg tablet taken twice daily. Of note, in clinical trials a dose of 10 mg once daily was studied and found to have almost as much weight loss at the twice-daily dose. Therefore, if this medication appears appropriate for a person, the twice-daily dosing scheme should not be a barrier since it may be possible to have similar efficacy if the second dose is occasionally missed. Specific dosage adjustments for renal and hepatic impairment are not provided, but the manufacturer does recommend avoiding use of lorcaserin in patients with severe renal or hepatic disease.

### Phentermine/Topiramate ER (Qsymia)

Phentermine is known as an anorectic, which is a type of medication that works in the hypothalamus to increase satiety. Topiramate’s exact mechanism to promote weight loss is unclear, but it is thought to work to both decrease appetite and increase satiety through action at multiple receptors.

Side effects are varied and are more prevalent with increased dosages. Side effects that occurred in more than 10 percent of patients at the highest dosage of phentermine/topiramate ER include: paresthesia, headache, constipation, dry mouth, and upper respiratory tract infections. Other side effects that occurred frequently include insomnia and dysgeusia (which most often lead to a metallic taste in the mouth).

The FDA has required a risk evaluation and mitigation strategy (REMS) due to the risk that phentermine/topiramate ER poses to a fetus. Topiramate is a known teratogen and there is increased risk for cleft palate formation if topiramate is used during a pregnancy. The REMS program requires prescribers of phentermine/topiramate ER to complete training that reviews the need to counsel females of reproductive age on the risks of birth defects, appropriate pregnancy testing, and the recommended contraceptive options. Pregnancy testing should be completed prior to initiating treatment and monthly during use. Additionally, pharmacies must become certified to dispense phentermine/topiramate ER by completing an online program and registering with the manufacturer. Information for dispensing pharmacists is available at [http://qsymiarems.com/information-for-pharmacists.htm](http://qsymiarems.com/information-for-pharmacists.htm).

Many drug interactions have been identified that are associated with the use of phentermine/topiramate ER. It is important to investigate these interactions prior to

<table>
<thead>
<tr>
<th>Table 4: Select Interactions to Screen When Initiating Lorcaserin</th>
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<tbody>
<tr>
<td><strong>Increased risk of serotonin syndrome</strong></td>
</tr>
<tr>
<td>SSRI</td>
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<tr>
<td>SNRI</td>
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<tr>
<td>MAOI</td>
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<tr>
<td>TCA</td>
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<tr>
<td>mirtazapine</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Triptans</td>
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<tr>
<td>Dextromethorphan</td>
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<tr>
<td>Tramadol</td>
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<tr>
<td>St. John’s Wort</td>
</tr>
</tbody>
</table>

*Not all drugs within a class may be affected. Refer to package insert of drug in question.
prescribing or dispensing this medication. One of the more common interactions that might be encountered during clinical practice is with metformin. When the highest dose of phentermine/topiramate ER is used in combination with metformin 500 mg BID, a 23 percent increase in area under the curve for metformin is observed. The clinical effects of this interaction are unclear, but dosage adjustments for metformin may be considered if side effects or safety concerns for high-dose metformin are a concern.

The dosing for phentermine/topiramate ER is detailed and somewhat complicated. There are a total of four different dosing steps for this medication and two instances where evaluation will help influence dosing changes. An initial dose of 3.75 mg/23 mg should be used for the first 14 days of therapy, and after this time, the patient should be transitioned to the 7.5 mg/46 mg dose. After 12 weeks of this increased dose, the patient’s weight should be evaluated. If at this time weight loss is 3 percent or greater, the patient may continue at the current dose. If weight loss is less than 3 percent, a decision should be made to either discontinue treatment or to increase the dosage. If the dosage is increased, a two-week dosage of 11.25 mg/69 mg should be prescribed and followed by a 12-week prescription for 15 mg/92 mg dose. If after 12-weeks of treatment at the highest dose (15 mg/92 mg) the patient has not lost 5 percent body weight, phentermine/topiramate ER should be discontinued. Of note, when phentermine/topiramate ER is discontinued from the highest dose, a taper of one dose every other day for one week should be used to decrease the risk of seizure.

**Naltrexone/Bupropion ER (Contrave)**

Naltrexone/bupropion is thought to work through two complementary mechanisms. One site of action is the hypothalamus, which helps to regulate the appetite, and the other action is through the mesolimbic dopamine circuit, which can be referred to as the “reward center.”

Adverse reactions that occurred in more than 10 percent of patients in clinical trials included nausea, constipation, headache, and vomiting. It is also important to be aware of less common, but more concerning adverse reactions. Many antidepressants come with labeling for increased risk of suicidal ideation and the inclusion of bupropion in this medication means that naltrexone/bupropion ER also carries this risk; appropriate monitoring should be conducted. Additionally, bupropion is known to lower the seizure threshold and so this medication should not be used in people with pre-existing seizure disorders. Care should be taken not to exceed the recommended dosages or titrate more quickly than recommended so as to not further increase risk for seizures.

Several drug interactions exist for patients taking naltrexone/bupropion ER. Because naltrexone is an opioid antagonist, this medication should not be taken concomitantly with opioids. Naltrexone/bupropion ER administration can be temporarily held if a short-term treatment of opioids is needed, but if chronic opioid treatment is initiated, naltrexone/bupropion ER should be discontinued. Of note, a patient’s sensitivity to opioids may be increased after taking naltrexone/bupropion ER, so lower doses of opioids should be initiated. Additionally, bupropion use concomitantly with monoamine oxidase inhibitors (MAOI) is contraindicated, and administration of these two medications should be separated by at least 14 days to avoid the risk of hypertensive reactions.

Each pill contains 8 mg naltrexone and 90 mg bupropion ER. The dose of naltrexone/bupropion ER is increased each week for the first month of therapy; patients initiate the medication by taking one pill daily for the first week, increase to one pill twice daily during week two, and then during week three add another pill in the morning, and complete the titration at week four when they are taking two pills twice daily. For patients with moderate-severe renal impairment, the maximum dose is one tablet BID, and for those with hepatic impairment, the maximum dose is one tablet daily. Patients should be advised to not take naltrexone/bupropion ER with a high fat meal as the concentrations of both naltrexone and bupropion increased significantly when patients took these medications with high fat meals.

**Liraglutide (Saxenda)**

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 helps to control appetite and is degraded by endogenous enzymes within minutes of production. Liraglutide is formulated to be more stable and not break down as quickly as GLP-1. It was originally developed and is still used as a medication for diabetes (Victoza at a dose of 1.2 or 1.8 mg daily), but has been approved by the FDA for use at higher doses (3 mg daily) for weight loss.

The most common side effects associated with liraglutide are gastrointestinal in nature. Nausea, diarrhea, constipation, and vomiting all occurred in more than 10 percent of patients in clinical trials. In general, patients described these adverse effects as mild-moderate and noted that they improved with time. A total of 6.2 percent of patients discontinued liraglutide in clinical trials as a result of these adverse effects as mild-moderate and noted that they improved with time. A total of 6.2 percent of patients discontinued liraglutide in clinical trials as a result of gastrointestinal adverse events (versus 0.8 percent of patients treated with placebo). The liraglutide label has a boxed warning describing the risk of thyroid c-cell tumors based on studies in rats and mice, though it is unknown if it causes this cancer in humans. Other adverse events to monitor for include injection site reactions and hypoglyce-
mia (which is most commonly seen in patients with type 2 diabetes on insulin or sulfonylurea therapy).

There are relatively few known drug interactions with liraglutide. Dosage adjustments in insulin secretagogues (such as glipizide, glyburide) are recommended. When initiating liraglutide, the manufacturer suggests initially decreasing the dose of the secretagogue in half and monitoring blood sugars closely.

Liraglutide for weight loss is supplied in a pre-filled pen that can deliver five different dosage forms. The first week of therapy should consist of the lowest dosage (0.6 mg). The patient should be instructed to increase the dosage by 0.6 mg weekly until he or she reaches the full dose of 3 mg. The full dose should be initiated at the start of week five. The dose is escalated slowly simply to decrease the gastrointestinal side effects associated with liraglutide. If the patient is having trouble tolerating the dose increase, consideration should be given to waiting an additional week prior to increasing the dose further. If the patient misses three doses in a row, they should be instructed to start back at 0.6 mg as if they were re-initiating the medication and once again increase the weekly dose.

Liraglutide is injected subcutaneously and can be administered in the abdomen, thigh, or upper arm. It can be given without respect to meals. Pens should be stored in the refrigerator until the expiration date on the package, but once they are started they can be stored at room temperature for up to 30 days.

**COMPARISON OF OBESITY MEDICATIONS**

When considering weight loss medications for patients, it is important to review variations that exist between medications. One of the first potential differences that may come to mind is the efficacy of the medication. Since these medications are relatively new, the main outcome that is available to judge efficacy is weight loss (for many medications, there are ongoing cardiovascular outcomes trials).

Table 6 outlines the percentage of patients who were able to achieve clinically meaningful weight loss (often defined as 5 percent weight loss in three months) during clinical trials. When interpreting these numbers, it is important to keep in mind that these were not generated from head-to-head trials. The different clinical trials from which these data were generated enrolled patients of different backgrounds and also provided patients with different levels of support to make lifestyle changes. Therefore, this efficacy data should not be viewed as a definitive comparison among the medications, but instead as a guideline about general weight loss that can be achieved for individual medications when combined with lifestyle interventions.

Administration of medications is another important consideration when choosing an obesity medication. Liraglutide is unique from the other obesity medications in that it is an injectable. However, it is administered once daily, which is

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
<th>Patient Pearls</th>
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| Orlistat                | “Doesn’t allow your body to absorb fat”          | • Take a multivitamin at least 2 hours before or after administration.  
|                         |                                                  | • Take during each meal (can take up to one hour after meal).  
|                         |                                                  | • Skip if skipping a meal or eating a no fat meal.                  |
| Lorcaserin              | “Makes you feel full”                           | • This medication interacts with other medications (especially those used for depression), so let us know when you start new medications. |
| Phentermine/topiramate ER| “Makes you feel full and also decreases your appetite” | • Take in the morning so the medication won’t keep you up at night.  
|                         |                                                  | • This medication shouldn’t be suddenly stopped. We can help you with a plan to discontinue the medication, if needed. |
| Naltrexone/bupropion ER  | “Decreases your appetite”                        | • Do not take with a high fat meal.  
|                         |                                                  | • This medication interacts with several medications (especially those used for pain), so let us know when you start new medications. |
| Liraglutide             | “Decreases your appetite”                        | • Inject in your abdomen, thigh, or upper arm.  
|                         |                                                  | • If you miss more than 3 doses in a row, start your dosing back at week 1 and increase the dose in the same way you did when you started the medication. |
a benefit for many patients. Lorcaserin and phentermine/topiramate ER are the other once daily medications and of them, lorcaserin allows for the most flexible dosing times as it can be administered at any time. Phentermine/topiramate ER should be administered in the morning because phentermine is a stimulant. Lastly, naltrexone/bupropion ER is administered twice daily and orlistat is administered up to three times daily; these two medications may not be ideal for someone who is not accustomed to taking a medication several times daily.

Another consideration when comparing the various obesity medications is any concomitant diseases the patient may have. Diabetes is one of the more common diseases that coexists with obesity, and when considering weight loss medications, liraglutide is the only option that is approved to treat both diseases. The Endocrine Society guidelines recommend preferentially considering liraglutide—after metformin has been maximized—for treatment of diabetes in patients who are obese. As was highlighted in the details for each individual medication, there are certain disease states and drug interactions that would cause the practitioner to avoid a particular obesity medication in specific populations. In brief, orlistat should not be used in patients that have irritable bowel disease or other conditions that might make the gastrointestinal side effects of the medication particularly uncomfortable. Patients who are taking serotonin modulating medications may not be the best candidates for lorcaserin, and if lorcaserin is used in these instances, extreme caution should be taken to identify serotonin syndrome. Naltrexone/bupropion ER should be avoided in patients who are taking chronic opioids and also for those who have seizure disorders. Although there are many other disease-specific considerations, the ones highlighted above are likely some of the more common issues that will arise.

ENDOCRINE SOCIETY RECOMMENDATIONS AND CONCLUSION

The Endocrine Society published guidelines in January 2015 about the use of pharmacologic agents for the treatment of obesity. Key concepts from these guidelines are summarized as follows.

In discussing medications, the Endocrine Society recommends that when pharmacologic treatment is used, it should be in addition to lifestyle changes. Further, these guidelines recommend that pharmacologic treatment should be used—when indicated—to decrease effects from comorbidities and to help enhance a person’s ability to adhere to lifestyle changes.

Monitoring parameters outlined by the manufacturers for these medications are reinforced by the guidelines. Namely, the recommendations to discontinue these medications if not effective in the first three months (see Table 3) are supported. Additional medication monitoring parameters include assessing efficacy and safety every month for the first three months of therapy and then every three months thereafter.

These guidelines also discuss medication selection for people with certain disease states. For instance, it is recommended that patients with type 2 diabetes who are overweight or obese should preferentially use diabetic medications that help to decrease weight (such as GLP-1 agonists or SGLT-2 inhibitors) in addition to metformin. Additionally, for those patients with a cardiovascular disease and an indication for a chronic obesity medication, it is recommended to avoid sympathomimetics, and instead choose medications such as orlistat or lorcaserin.

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<table>
<thead>
<tr>
<th>Table 6: Patients Who Achieved Clinically Meaningful Weight Loss</th>
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<tr>
<td><strong>Weight Loss</strong></td>
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<tr>
<td>Orlistat</td>
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<tr>
<td>Lorcaserin</td>
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<td>Phentermine/topiramate ER</td>
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Editor’s Note: For the list of references used in this article, please contact America’s Pharmacist Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.
Continuing Education Quiz
Select the correct answer.

1. Which of the following patients is considered obese?
   a. A female who is 5 feet 5 inches (1.65 meters) and 170 pounds (77 kilograms).
   b. A male who is 5 feet 7 inches (1.70 meters) and 195 pounds (88 kilograms).
   c. A female who is 5 feet 2 inches (1.57 meters) and 150 pounds (68 kilograms).
   d. A male who is 6 feet 2 inches (1.88 meters) and 225 pounds (102 kilograms).

2. Obese patients experience how much more in increased prescription costs compared to their non-obese counterparts?
   a. 20 percent more
   b. 50 percent more
   c. 80 percent more
   d. 150 percent more

3. A patient asks you how his waist size relates to his health. What is a correct answer?
   a. You should be monitoring your BMI and not your waist size because a BMI that indicates obesity is tied with increased risk of death.
   b. If you are overweight or obese, as your waist size increases, your risk for heart disease and death increases.
   c. Waist size is important and we recommend monitoring it every five years.
   d. Waist size is not important to your health.

4. In an adult patient who is 260 pounds (BMI 32 kg/m^2), what is the smallest amount of sustained weight loss that can lead to clinically meaningful results?
   a. 3-5 pounds
   b. 8-13 pounds
   c. 13-26 pounds
   d. 26-52 pounds

5. Which of the following patients do the AHA/ACC/TOS guidelines recommend as a candidate for bariatric surgery?
   a. Any obese patient (BMI ≥ 30 kg/m^2)
   b. BMI ≥ 25 kg/m^2 or ≥ 30 kg/m^2 with comorbidities
   c. BMI ≥ 30 kg/m^2 or ≥ 35 kg/m^2 with comorbidities
   d. BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with comorbidities

6. Which medication for diabetes can lead to weight loss?
   a. Glipizide
   b. Insulin glargine
   c. Canagliflozin
   d. Pioglitazone

7. Which antidepressant is associated with weight loss?
   a. Amitriptyline
   b. Bupropion
   c. Mirtazapine
   d. Paroxetine

8. One of your patients has questions about medications for chronic weight management. He wonders if he is a candidate for a medication. He is 42 years old and tells you he is 6 feet tall and weighs 210 pounds. He tells you he has depression and seasonal allergies. Is this patient a candidate for one of the chronic weight loss medications presented in this article?
   a. Yes
   b. No, because weight loss pharmacotherapy is contraindicated in patients with depression.
   c. No, because the patient does not meet the criteria for initiation of pharmacotherapy.

9. A patient presents for her fourth prescription of lorcaserin; she has filled the medication consistently for three full months. She tells you that she has lost six pounds since she started lorcaserin (at that time she weighed 180 pounds) and is wondering if she should keep taking lorcaserin. What should you tell her?
   a. We generally give the medication four full months before we evaluate its effect.
   b. You have lost over 3 percent of your body weight, which means you should continue the medication.
   c. You haven’t lost 5 percent of your body weight so at this point, we think the medication likely isn’t effective.
   d. This is a medication that is used chronically so you shouldn’t stop the medication.

10. What advice is NOT recommended per the package labeling for orlistat?
    a. Skip the dose if you are eating a meal that doesn’t contain fat.
    b. If you only eat two meals per day, take orlistat twice – once with each meal.
    c. Take half your dose with each snack.
    d. Add a multivitamin to your medication regimen if you’re on orlistat.
11. Which medication is contraindicated in pregnancy?
   a. Lorcaserin
   b. Phentermine/Topiramate
   c. Naltrexone/Bupropion
   d. All of the above

12. A 28-year-old female with a BMI of 32 kg/m2 is interested in starting a medication for obesity. She notes that she has anxiety and insomnia. She has been consistently taking escitalopram 20 mg daily and melatonin 3 mg daily. Which medication would you avoid in this patient due to drug-drug interactions?
   a. Orlistat
   b. Lorcaserin
   c. Phentermine/Topiramate
   d. Liraglutide

13. Which medication is contraindicated in someone with seizure disorders?
   a. Lorcaserin
   b. Phentermine/Topiramate
   c. Naltrexone/Bupropion
   d. Liraglutide

14. One of the providers you work with wants to start an obesity medication for a patient, but wants the titration schedule to be as simple as possible. If she based the decision solely on a simple titration schedule, which medication should she select?
   a. Lorcaserin
   b. Phentermine/Topiramate
   c. Naltrexone/Bupropion
   d. Liraglutide

15. A local prescriber calls you to discuss a patient. The patient is taking liraglutide for weight loss and has just completed week three of the titration schedule (1.8 mg), but believes he has not adapted to the nausea that started at the beginning of week three. The prescriber wonders what should be done to help. What is the best response?
   a. The patient can continue for another week taking the week three (1.8 mg daily) dose before titrating up to the week four dose (2.4 mg daily).
   b. The patient can start back at the week one (0.6 mg daily) dose and then continue the recommended titration schedule.
   c. The patient should be initiated on ondansetron and escalate the dose to the week four dose (2.4 mg daily) today.
   d. The patient should discontinue this medication and try another medication for obesity.

16. What is the risk of discontinuing phentermine/topiramate ER without a taper?
   a. Extreme nausea
   b. Hypoglycemia
   c. Seizure
   d. Serotonin syndrome

17. Which of the following is true about the efficacy of the medications for weight loss presented in this article?
   a. Data regarding mortality effects as a result of these medications is not available.
   b. When phentermine/topiramate ER and lorcaserin are compared head-to-head, more weight loss is achieved with phentermine/topiramate.
   c. Because the medications are for long-term use, no efficacy measures can be evaluated until a patient has completed one year of therapy.
   d. All of the above

18. Why do the Endocrine Society guidelines recommend use of obesity medications?
   a. To decrease mortality and increase adherence to lifestyle changes
   b. To decrease mortality and decrease effects from comorbidities
   c. To decrease effects from comorbidities and increase adherence to lifestyle changes
   d. None of the above

19. You receive a prescription for a 26-year-old female for phentermine/topiramate ER 11.25 mg/69 mg take one by mouth at night QHS #30; 0 refills. She is taking no other medications. What question(s) may you have for the provider?
   a. This dose is only approved to be used as a titration step for two weeks. Do you want to change the days supply to 14?
   b. This medication should be taken in the morning. Would you like me to change the directions?
   c. What did you and the patient discuss for contraception options?
   d. All of the above

20. A patient tells you she started taking orlistat two weeks ago for weight loss. She asks you for more information about flatus and oily spotting since she is experiencing these side effects with orlistat. What can you tell her?
   a. Attempt to eat lower fat meals since the side effects from orlistat are more pronounced with high fat meals.
   b. Those side effects are known to improve over time.
   c. Unfortunately, there are no tricks to decreasing these side effects.
   d. A and B