Obesity Pharmacotherapy

Katherine H. Saunders, MD, DABOM*, Devika Umashanker, MD, MBA, Leon I. Igel, MD, DABOM, Rekha B. Kumar, MD, MS, DABOM, Louis J. Aronne, MD, DABOM, FTOS

KEYWORDS

• Obesity • Weight management • Pharmacotherapy • Orlistat
• Phentermine/topiramate • Lorcaserin • Naltrexone/bupropion • Liraglutide

KEY POINTS

- Although diet, physical activity, and behavioral modifications are the cornerstones of weight management, weight loss achieved by lifestyle modifications alone is often limited and difficult to maintain.
- Pharmacotherapy for obesity can be considered if patients have a body mass index (BMI) of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 or greater with weight-related comorbidities.
- The 6 most commonly used antiobesity medications are phentermine, orlistat, phentermine/topiramate extended release, lorcaserin, naltrexone sustained release (SR)/bupropion SR, and liraglutide 3.0 mg.
- It is important for primary care providers to be familiar with the pharmacotherapy available to patients who cannot lose weight and sustain weight loss with lifestyle interventions alone.
- Successful pharmacotherapy for obesity depends on tailoring treatment to patients' behaviors and comorbidities as well as close monitoring of efficacy, safety, and tolerability.

INTRODUCTION

Diet, physical activity, and behavioral modifications are the cornerstones of weight management.[1] However, weight loss achieved by lifestyle modifications alone is often limited and difficult to maintain. Reduced caloric intake and increased energy

Disclosure Statement: K.H. Saunders, D. Umashanker, and L.I. Igel have no conflicts of interest. R.B. Kumar is a speaker for Janssen Pharmaceuticals and Novo Nordisk A/S. She is a shareholder in Zafgen, VIVUS, and MYOS Corporation. L.J. Aronne has received research funding from Aspire Bariatrics, Eisai, and Takeda Pharmaceuticals. He declares consultant/advisory board work with Jamieson Labs, Pfizer Inc, Novo Nordisk A/S, Eisai, VIVUS, GI Dynamics, JOVIA Health, and Gelesis. He is a shareholder of Zafgen, Gelesis, MYOS Corporation, and Jamieson Labs, and he is on the board of directors of MYOS Corporation and Jamieson Labs.

Comprehensive Weight Control Center, Division of Endocrinology, Diabetes, and Metabolism, Weill Cornell Medicine, 1165 York Avenue, New York, NY 10065, USA
* Corresponding author.
E-mail address: kph2001@med.cornell.edu

Med Clin N Am 102 (2018) 135–148
https://doi.org/10.1016/j.mcna.2017.08.010 **medical.theclinics.com**

expenditure are counteracted by adaptive physiologic responses.[2] Not only does appetite increase but resting metabolic rate slows out of proportion to what would be expected based on changes in body composition.[3] This phenomenon, called adaptive thermogenesis or metabolic adaptation, impedes weight loss and contributes to weight regain.[4,5]

Antiobesity pharmacotherapy is one strategy to offset the adaptive changes in appetite and energy expenditure that occur with weight loss and to improve adherence to lifestyle interventions.[3] According to the 2013 American College of Cardiology/American Heart Association/The Obesity Society's guideline for the management of overweight and obesity in adults and the Endocrine Society's clinical practice guidelines on the pharmacologic management of obesity, pharmacotherapy for obesity can be considered if patients have a body mass index (BMI) of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 or greater with weight-related comorbidities, such as hypertension, dyslipidemia, type 2 diabetes, and obstructive sleep apnea.[1,6]

As obesity is a chronic disease, most antiobesity medications are approved for long-term treatment. Until a few years ago, phentermine (and other sympathomimetic amines) and orlistat were the only antiobesity medications approved by the Food and Drug Administration (FDA). In 2012, phentermine/topiramate extended release (ER) and lorcaserin were approved; in 2014, naltrexone sustained release (SR)/bupropion SR and liraglutide 3.0 mg were approved.

In this article, the authors review the 6 most widely used antiobesity medications (**Table 1**). The authors present efficacy and safety findings, discuss how to best select agents for each patient, and provide advice on how to manage patients who do not respond to medications. Although referral to an obesity medicine specialist is an option for some primary care providers, there are not enough obesity medicine specialists to address the obesity epidemic. Therefore, it is important for primary care providers to be familiar with the pharmacotherapy available to patients who are unable to lose weight and sustain weight loss with lifestyle interventions alone.

PHENTERMINE

Phentermine was approved by the FDA in 1959 and has been the most commonly prescribed medication for obesity in the United States. It is an adrenergic agonist that increases resting energy expenditure and suppresses appetite. Phentermine is indicated for short-term use (3 months), as there are no long-term safety trials of phentermine monotherapy; but it was approved in combination with topiramate ER for long-term therapy. Many practitioners prescribe phentermine for greater than 3 months as off-label therapy for ongoing weight management.

Two other sympathomimetic amines, diethylpropion and phendimetrazine, are also available in the United States; but data on these agents are minimal, and they are prescribed much less frequently.

Until recently, the available doses of phentermine were 15.0, 30.0, and 37.5 mg.[7–9] As prescribing practices should be individualized to determine the lowest effective dose, many practitioners recommend using quarter or half tablets of these formulations. In 2016, the FDA approved an 8-mg formulation, which can be prescribed up to 3 times daily.[10] Administration of the last dose late in the day should be avoided to prevent insomnia. Phentermine is a schedule IV controlled substance.

In a 28-week randomized controlled trial comparing phentermine, topiramate ER, and the combination of the two agents, phentermine 15 mg daily produced an average 6.0-kg weight loss compared with a 1.5-kg weight loss with placebo.[11] Forty-six percent of participants assigned to phentermine lost at least 5% of initial body weight

Table 1
Antiobesity medications

Medication	Mechanism, Dosage, and Available Formulations	Trial and Duration	Trial Arms	Weight Loss (%)	Most Common Adverse Events	Consider This Medication in These Patients	Avoid This Medication in These Patients
Phentermine[7–10] Schedule IV controlled substance NOTE: approved for short-term use	Adrenergic agonist 8.0 mg–37.5 mg daily (8-mg dose can be prescribed up to TID) Capsule, tablet	Aronne LJ, et al[11] 28 wk	15 mg daily 7.5 mg daily Placebo (topiramate ER and phentermine/ topiramate ER arms excluded)	6.06[a] 5.45[a] 1.71	Dry mouth, insomnia, dizziness, irritability	Younger patients who need assistance with appetite suppression	Patients with uncontrolled hypertension, active or unstable coronary disease, hyperthyroidism, glaucoma, anxiety, insomnia, or patients who are generally sensitive to stimulants; patients with a history of drug abuse or recent MAOI use; patients who are pregnant
Orlistat[14,15]	Lipase inhibitor 60–120 mg TID with meals Capsule	XENDOS[16] 208 wk	120 mg TID Placebo	9.6 (wk 52)[a] 5.25 (wk 208)[a] 5.61 (wk 52) 2.71 (wk 208)	Fecal urgency, oily stool, flatus with discharge, fecal incontinence	Patients with hypercholesterolemia and/or constipation who can limit their intake of dietary fat	Patients with malabsorption syndromes or other GI conditions that predispose to GI upset/diarrhea; patients who cannot modify the fat content of their diets; patients who are pregnant

(*continued on next page*)

Table 1
(*continued*)

Medication	Mechanism, Dosage, and Available Formulations	Trial and Duration	Trial Arms	Weight Loss (%)	Most Common Adverse Events	Consider This Medication in These Patients	Avoid This Medication in These Patients
Phentermine/ topiramate ER[19] Schedule IV controlled substance	Adrenergic agonist/neuro-stabilizer 3.75/23–15/92 mg daily (dose titration) Capsule	EQUIP[21] 56 wk	15/92 mg daily 3.75/23 mg daily Placebo	10.9[a] 5.1[a] 1.6	Paresthesias, dizziness, dysgeusia, insomnia, constipation, dry mouth	Younger patients who need assistance with appetite suppression	Patients with uncontrolled hypertension, active or unstable coronary disease, hyperthyroidism, glaucoma, anxiety, insomnia, or patients who are generally sensitive to stimulants; patients with a history of drug abuse or recent MAOI use; patients with a history of nephrolithiasis; patients who are pregnant or trying to conceive
		CONQUER[22] 56 wk	15/92 mg daily 7.5/46 mg daily Placebo	9.8[a] 7.8[a] 1.2			
		SEQUEL[23] 108 wk (52-wk extension of CONQUER trial)	15/92 mg daily 7.5/46 mg daily Placebo	10.5[a] 9.3[a] 1.8 (wk 0–108)			

Lorcaserin[25] Schedule IV controlled substance	Serotonin (5HT-2C) receptor agonist 10 mg BID or 20 mg XR daily Tablet	BLOOM[27] 52 wk	10 mg BID Placebo	5.8[a] 2.2	Headache, dizziness, fatigue, nausea, dry mouth, constipation	Patients who would benefit from appetite suppression	Patients on other serotonin-modulating medications and patients with known cardiac valvular disease; patients who are pregnant
		BLOSSOM[29] 52 wk	10 mg BID 10 mg daily Placebo	5.8[a] 4.7[a] 2.8			
		BLOOM-DM[28] 52 wk	10 mg BID 10 mg daily Placebo	4.5[a] 5.0[a] 1.5			
Naltrexone/ bupropion SR[43]	Opioid receptor antagonist/ dopamine and norepinephrine reuptake inhibitor 8/90 mg daily to 16/180 mg BID Tablet	COR-I[32] 56 wk	16/180 mg BID 8/180 mg BID Placebo	6.1[a] 5.0[a] 1.3	Nausea, vomiting, constipation, headache, dizziness, insomnia, dry mouth	Patients who describe cravings for food and/ or addictive behaviors related to food; patients who are trying to quit smoking, reduce alcohol intake, and/or have concomitant depression	Patients with uncontrolled hypertension, uncontrolled pain, recent MAOI use, history of seizures, or any condition that predisposes to seizure, such as anorexia/bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; patients who are pregnant
		COR-II[33] 56 wk	16/180 mg BID Placebo	6.4[a] 1.2			
		COR-BMOD[34] 56 wk	16/180 mg BID Placebo	9.3[a] 5.1			
		COR-Diabetes[35] 56 wk	16/180 mg BID Placebo	5.0[a] 1.8			

(*continued on next page*)

Table 1
(*continued*)

Medication	Mechanism, Dosage, and Available Formulations	Trial and Duration	Trial Arms	Weight Loss (%)	Most Common Adverse Events	Consider This Medication in These Patients	Avoid This Medication in These Patients
Liraglutide 3.0 mg[44]	GLP-1 receptor agonist 0.6–3.0 mg daily Prefilled pen for subcutaneous injection	SCALE Obesity and Prediabetes[38] 56 wk	3.0 mg daily Placebo	8.0[a] 2.6	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain	Patients who report inadequate meal satiety and/or have type 2 diabetes, prediabetes, or impaired glucose tolerance; patients requiring use of concomitant psychiatric medications	Patients with a history of pancreatitis, personal/family history of MTC or MEN2; patients with an aversion to needles; patients who are pregnant
		SCALE Diabetes[37] 56 wk	3.0 mg daily 1.8 mg daily Placebo	6.0[a] 4.7[a] 2.0			
		SCALE Maintenance[39] 56 wk (after initial ≥5% weight loss with LCD)	3.0 mg daily Placebo	6.2[a] 0.2			

Abbreviations: BID, twice daily; 5HT, 5-hydroxytryptamine; GI, gastrointestinal; GLP-1, glucagonlike peptide-1; LCD, low-calorie diet; MAOI, monoamine oxidase inhibitor; MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; TID, 3 times daily; XR, extended release.

[a] $P < .001$ versus placebo.

Adapted from Igel LI, Kumar RB, Saunders KH, et al. Practical use of pharmacotherapy for obesity. Gastroenterology 2017;152(7):1765–79; and Saunders KH, Kumar RB, Igel LI, et al. Pharmacologic approaches to weight management: recent gains and shortfalls in combating obesity. Curr Atheroscler Rep 2016;18(7):36; with permission.

and 20.8% lost at least 10% of initial body weight, whereas 15.5% and 6.8% of subjects assigned to placebo achieved at least 5% and 10% weight loss, respectively.

Interestingly, there seems to be no advantage of continuous compared with intermittent phentermine treatment, at least on a short-term basis. A 36-week, double-blind, placebo-controlled trial compared continuous phentermine, continuous placebo, and alternating phentermine/placebo every 4 weeks.[12] The mean weight loss was 12.2 kg and 13.0 kg in patients who received phentermine continuously and intermittently, respectively, compared with 4.8-kg weight loss in the placebo group. The weight loss in this study was higher than expected, as data were presented for completers only.

The most common treatment-emergent adverse events (TEAEs) include headache, dry mouth, insomnia, dizziness, irritability, nausea/vomiting, diarrhea, and constipation. Phentermine should not be prescribed in combination with other sympathomimetic amines or with monoamine oxidase inhibitors (MAOIs). Contraindications include pregnancy/nursing, history of cardiovascular disease or drug abuse, hyperthyroidism, glaucoma, and agitated states.

ORLISTAT

Before 2012, the only antiobesity medicine approved for long-term use was orlistat, which was approved by the FDA in 1999. Orlistat is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. It is also indicated to reduce the risk of weight regain after prior weight loss.

Orlistat promotes weight loss by inhibiting pancreatic and gastric lipases, thereby decreasing the absorption of fat from the gastrointestinal tract. On average, 120 mg of orlistat taken 3 times per day with meals decreases fat absorption by 30%.[13]

The recommended dosage of orlistat is one 120-mg capsule or one 60-mg capsule 3 times per day with each meal containing fat.[14,15] The medication can be taken during a meal or up to 1 hour after food consumption. Patients on orlistat should be advised to follow a nutritionally balanced, reduced-calorie diet with approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over 3 meals. Patients should take a multivitamin (separately from the medication) while on orlistat, as it can decrease the absorption of fat-soluble vitamins (A, D, E, K).

In a double-blind prospective study that randomized 3305 patients with a BMI of 30 kg/m^2 or greater to lifestyle changes with either orlistat 120 mg or placebo 3 times daily, the mean weight loss was significantly greater with orlistat (5.8 kg) than with placebo (3.0 kg) after 4 years.[16] Fifty-three percent of the patients assigned to orlistat lost 5% or greater of their initial body weight, and 26.2% lost 10% or greater of their initial body weight.

In addition to promoting weight loss, orlistat lowers serum glucose levels and improves insulin sensitivity. The cumulative incidence of diabetes in the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) trial was 6.2% with orlistat and 9.0% with placebo, which corresponds to a risk reduction of 37.3%. Orlistat has also been found to improve blood pressure, total cholesterol, and low-density lipoprotein cholesterol.[17]

Orlistat is not commonly used for obesity management because of the side effects of fecal urgency, oily stool, and fecal incontinence; but it may have a role as an additional medicine for patients who are constipated on other antiobesity pharmacotherapy. A slow dose titration or the addition of a psyllium fiber supplement can reduce side effects.

Orlistat should not be used in patients who are pregnant or who have chronic malabsorption syndromes or cholestasis. Orlistat can decrease the absorption of medications, such as cyclosporine, levothyroxine, warfarin, amiodarone, antiepileptic agents, and antiretroviral drugs.

PHENTERMINE/TOPIRAMATE EXTENDED RELEASE

In 2012, the FDA approved phentermine/topiramate ER for chronic weight management as an adjunct to a reduced-calorie diet and increased physical activity. The rationale for a combination medication is that appetite regulation involves multiple pathways, so targeting different mechanisms simultaneously can have an additive effect on body weight. Another benefit is that the smaller dose of each medication reduces the risk of TEAEs.

Topiramate was approved for epilepsy in 1996 and migraine prophylaxis in 2004. The medication's effect on caloric intake is thought to be mediated through modulation of gamma-aminobutyric acid receptors, inhibition of carbonic anhydrase, and antagonism of glutamate.[18]

Phentermine/topiramate ER is available in 4 doses (3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15.0/92 mg), which are lower than the maximum doses of the individual agents.[19] The medication should be taken once daily in the morning with or without food. After 14 days of 3.75/23 mg daily, patients can progress to 7.5/46 mg daily. Phentermine/topiramate ER should be discontinued or the dose should be escalated if 3% weight loss is not achieved after 12 weeks. For escalation, a titration dose of 11.25/69 mg is taken daily for 2 weeks and then increased to 15/92 mg daily for maintenance. The medication should also be discontinued if 5% weight loss is not achieved after 12 additional weeks on 15/92 mg daily.

Phentermine/topiramate ER is a schedule IV controlled substance. The FDA requires a Risk Evaluation and Mitigation Strategy to inform prescribers and women of reproductive potential about the possible increased risk of orofacial clefts in infants exposed to phentermine/topiramate ER during the first trimester of pregnancy.[20]

Two randomized, double-blind, placebo-controlled trials, EQUIP and CONQUER, evaluated the efficacy of phentermine/topiramate ER over 56 weeks.[21,22] The CONQUER trial randomized 2487 patients with a BMI of 27 to 45 kg/m^2 and 2 or more comorbidities (hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity) to phentermine/topiramate ER 15/92 mg, phentermine/topiramate ER 7.5/46 mg, or placebo. Compared with placebo, both doses resulted in significantly greater weight loss (9.8 kg with 15/92 mg, 7.8 kg with 7.5/46 mg, and 1.2 kg with placebo). Seventy percent of patients achieved at least 5% weight loss with 15/92 mg compared with 62% with 7.5/46 mg and 21% with placebo.

The SEQUEL trial evaluated ongoing weight loss with phentermine/topiramate ER for 52 weeks after completion of the CONQUER study.[23] The mean percentage reduction in body weight was found to be significantly greater in the treatment groups compared with placebo (10.5%, 9.3%, and 1.8% with 15/92 mg, 7.5/46 mg, and placebo, respectively). The study also reported a 76% reduction in the progression to diabetes in subjects receiving 15/92 mg and a 54% reduction in subjects receiving 7.5/46 mg compared with placebo.

The most common TEAEs with phentermine/topiramate ER include paresthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Contraindications include pregnancy (a pregnancy test is recommended before starting followed by monthly tests in appropriate patients), glaucoma, hyperthyroidism, and MAOI use.

LORCASERIN

Lorcaserin, a selective serotonin (5-hydroxytryptamine [5HT])-2C receptor agonist, was approved by the FDA in 2012 as a long-term treatment of obesity. Lorcaserin reduces appetite and increases satiety by binding to the 5HT-2C receptors on anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus. Because of its selective agonism of the serotonin 2C receptor, lorcaserin was designed to avoid cardiac valvular effects mediated through the 5HT-2B receptor. The development program has not observed an increased incidence of valvulopathy over 2 years, and long-term data are being collected in a 5-year cardiovascular outcome study.[24]

The recommended dosage of lorcaserin is 10 mg twice daily with or without food.[25] There is also a new 20-mg extended release tablet, which can be taken once daily.[26] The medication should be discontinued if 5% or less weight loss is achieved after 12 weeks. Lorcaserin is a schedule IV controlled substance.

The phase III double-blind placebo-controlled Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial included 3182 adults who were overweight or obese and received lorcaserin 10 mg twice daily or placebo for 52 weeks, in conjunction with diet and exercise.[27] At week 52, all subjects treated with lorcaserin were rerandomized to either placebo or lorcaserin for an additional year. At 1 year, the average placebo-subtracted weight loss was 3.6%, and 47% of the subjects taking lorcaserin lost at least 5.0% as compared with 20.5% in the control group. Subjects who showed a weight loss of at least 5% in year 1 and were maintained on lorcaserin treatment in year 2 were able to maintain their weight loss better than those who had been switched to placebo.

The Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) study was conducted in subjects with obesity and type 2 diabetes.[28] At 52 weeks, 37.5% of patients treated with lorcaserin 10 mg twice daily showed a weight loss of at least 5%, which was more than twice the percentage in the placebo group. There was a reduction of hemoglobin A1c (HbA1c) of 0.9% in those on lorcaserin as compared with a 0.4% reduction in the placebo group.

The most common TEAEs include headache, dizziness, fatigue, nausea, dry mouth, and constipation.[27–29] There is a theoretic interaction with other serotonergic drugs, as coadministration may lead to the development of serotonin syndrome or neuroleptic malignant syndromelike reactions.

NALTREXONE SUSTAINED RELEASE/BUPROPION

Naltrexone/bupropion was approved for the treatment of obesity in 2014. Bupropion is a dopamine and norepinephrine reuptake inhibitor that was FDA approved as an antidepressant in 1989 and as a smoking cessation aide in 1997. Naltrexone is an opioid antagonist that was FDA approved for the treatment of opioid dependence in 1984 and alcohol use disorder in 1994.

Together, naltrexone/bupropion has effects in 2 separate areas of the brain involved in the regulation of food intake. One region is the arcuate nucleus of the hypothalamus, which is integral to appetite regulation. The second region is the mesolimbic dopamine reward circuit. By increasing the firing rate of hypothalamic POMC neurons while simultaneously modulating the dopamine reward circuit, both appetite and food cravings are reduced.[30,31]

Each tablet of naltrexone/bupropion contains 8 mg of ER naltrexone and 90 mg of ER bupropion. The initial prescription should be for one tablet daily in the morning with instructions to increase by one tablet weekly to a therapeutic dosage of 2 tablets twice

daily (32/360 mg). The medication should be discontinued if patients have achieved 5% or less weight loss at 16 weeks (after 12 weeks at the maintenance dose).

Four 56-week randomized double-blind placebo-controlled trials (COR-I, COR-II, Contrave Obesity Research Behavior Modification [COR-BMOD], and COR-Diabetes) were conducted to evaluate the effect of naltrexone/bupropion plus lifestyle modification in 4536 patients with overweight or obesity.[32–35] The COR-I, COR-II, and COR-BMOD trials enrolled patients with a BMI of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 or greater and at least one weight-related comorbidity. The COR-Diabetes trial enrolled patients with a BMI of 27 kg/m^2 or greater with type 2 diabetes with or without hypertension and/or dyslipidemia.

In the COR-I trial, the mean weight loss of 6.1% was observed in patients receiving naltrexone/bupropion 360/32 mg compared with 1.3% in patients receiving placebo; 48% of naltrexone/bupropion patients lost greater than 5% body weight from baseline as compared with 16% of placebo patients. In the COR-Diabetes trial, 44.5% of patients receiving naltrexone/bupropion lost 5% or greater of their body weight after 56 weeks compared with 18.9% of patients receiving placebo. Patients receiving naltrexone/bupropion demonstrated a 0.6% reduction in HbA1c from baseline compared with a 0.1% reduction in patients receiving placebo.

The most common side effects of naltrexone/bupropion include nausea/vomiting, constipation, headache, dizziness, insomnia, and dry mouth. Administration of naltrexone/bupropion with high-fat meals should be avoided, as this significantly increases the systemic levels of both bupropion and naltrexone. Naltrexone/bupropion is contraindicated in patients taking MAOIs or chronic opioids and in patients with uncontrolled hypertension, history of seizures, or conditions that predispose to seizure, such as anorexia or bulimia nervosa, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs. Bupropion carries a black box warning (as do all antidepressants) related to a potential increase in suicidality in patients younger than 24 years during the early phase of treatment, so patients should be monitored closely for mood changes when initiating naltrexone/bupropion.

LIRAGLUTIDE 3.0 MG

Liraglutide 3.0 mg was the second agent approved by the FDA in 2014 for chronic weight management. Liraglutide mimics the gastrointestinal incretin hormone, glucagonlike peptide-1, which is released in response to food intake. It is also FDA approved for the treatment of type 2 diabetes in doses up to 1.8 mg. Among patients with obesity and without diabetes, liraglutide 3.0 mg daily was found to reduce hunger, decrease food intake, and delay gastric emptying.[36]

Liraglutide is administered as a subcutaneous injection once daily. The starting dosage is 0.6 mg daily for 1 week with instructions to increase by 0.6 mg weekly to a therapeutic dosage of 3.0 mg daily. Slower dose titration can reduce gastrointestinal side effects. The medication should be discontinued if patients have not achieved at least 4% weight loss at 16 weeks.

Two phase III trials, SCALE Diabetes and SCALE Obesity and Prediabetes, evaluated the effect of liraglutide 3.0 mg on subjects who were overweight or obese with and without diabetes, respectively.[37,38] Both 56-week, randomized, placebo-controlled, double-blind trials illustrated significantly greater mean weight loss than placebo. In SCALE Diabetes, the mean weight loss was 6.0% with 3.0 mg daily, 4.7% with 1.8 mg daily, and 2.0% with placebo. In SCALE Obesity and Prediabetes, participants assigned to 3.0 mg daily lost a mean of 8.0% body weight compared with 2.6% in the placebo group.

The efficacy of liraglutide for weight maintenance was investigated in the SCALE Maintenance study.[39] Four hundred twenty-two subjects who were overweight or obese and had lost at least 5% of their initial body weight on a low-calorie diet were randomly assigned to liraglutide 3.0 mg daily or placebo for 56 weeks. The mean weight loss on the initial diet was 6.0%. By the end of the study, participants in the liraglutide group lost an additional 6.2% compared with 0.2% with placebo.

The most common TEAEs include nausea, vomiting, diarrhea, constipation, dyspepsia, and abdominal pain. Liraglutide is contraindicated in patients who are pregnant or those with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Thyroid C-cell tumors were found in rodents given supratherapeutic doses of liraglutide; however, there is no evidence of liraglutide causing C-cell tumors in humans. Concomitant use of liraglutide with insulin or insulin secretagogues can increase the risk of hypoglycemia.

PRACTICAL TIPS FOR TREATMENT

Since 2012, 4 new antiobesity medications have been approved. When patients are unable to lose and maintain weight loss with lifestyle interventions alone, providers should consider the use of pharmacotherapy to counteract metabolic adaptation and improve adherence to diet and exercise.[1,6]

There are 2 important questions to ask when prescribing an antiobesity medication to patients. The first question is whether there are undesirable side effects, contraindications, or drug-drug interactions. For example, avoid orlistat if patients have a condition predisposing to malabsorption and avoid phentermine and phentermine/topiramate ER if patients have unstable coronary disease.

The second question is whether any of the medications could improve another symptom or condition. For example, consider phentermine/topiramate ER if patients have migraines or naltrexone SR/bupropion SR if patients also would like assistance with smoking cessation. **Table 1** provides examples of ideal and poor candidates for each medication.

Pharmacotherapy should not be prescribed in the absence of behavioral counseling focusing on diet, physical activity, and lifestyle modifications, which are the cornerstones of weight management. Patients should be monitored at least monthly for the first 3 months of treatment and then at least once every 3 months.[6] Efficacy and safety should be assessed and behavioral interventions should be reinforced at each visit.

If a medication is determined to be ineffective or if there are safety or tolerability concerns at any time, the medication should be discontinued and alternative medications or treatment approaches should be pursued.[6] Another agent with a different mechanism of action can be considered.

Obesity pharmacotherapy is intended for long-term use, as obesity is a chronic disease. Continued use of medication promotes sustained weight maintenance by offsetting increased appetite and reduced energy expenditure secondary to the metabolic adaptation that occurs with weight loss. Once a desired weight has been achieved, reducing the dose or frequency of medication is a possible strategy that requires further study.

FUTURE CONSIDERATIONS

Many patients require more than one medication to achieve clinically significant weight loss. By targeting multiple pathways simultaneously, combination therapy can have an additive or synergistic effect on body weight. In addition to phentermine/topiramate ER

and naltrexone SR/bupropion SR, other combinations are under investigation, including phentermine/lorcaserin and phentermine/canagliflozin.[40,41] Instead of initiating 2 medications simultaneously, an alternative strategy is a stepwise approach in which an additional agent is added when patients reach a weight plateau.

Pharmacotherapy can be combined with bariatric surgery, both before and after the procedure. As weight regain after bariatric surgery is common, the addition of an antiobesity medication can be an effective tool to counteract recidivism and enhance weight maintenance.[42] Although data are limited, the optimal time to initiate antiobesity pharmacotherapy seems to be when patients reach a nadir weight instead of after weight regain has occurred. Finally, the combination of antiobesity pharmacotherapy with endoscopic procedures and devices is another area that requires further investigation.

REFERENCES

1. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. J Am Coll Cardiol 2014;63(25 Pt B):2985–3023.
2. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 2011;365(17):1597–604.
3. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes (Lond) 2015;39(8):1188–96.
4. Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. Int J Obes (Lond) 2010;34:S47–55.
5. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring) 2016;24(8):1612–9.
6. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100(2):342–62.
7. Adipex [package insert]. Tulsa, OK: Physicians Total Care, Inc; 2012.
8. Ionamin [package insert]. Rochester, NY: Celltech Pharmaceuticals, Inc; 2006.
9. Suprenza [package insert]. Cranford, NJ: Akrimax Pharmaceuticals, LLC; 2013.
10. Lomaira [package insert]. Newtown, PA: KVK-TECH, INC; 2016.
11. Aronne LJ, Wadden TA, Peterson C, et al. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity (Silver Spring) 2013;21(11):2163–71.
12. Munro JF, MacCuish AC, Wilson EM, et al. Comparison of continuous and intermittent anorectic therapy in obesity. Br Med J 1968;1(5588):352–4.
13. Zhi J, Melia AT, Guerciolini R, et al. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther 1994;56(1):82–5.
14. Xenical [package insert]. South San Francisco, CA: Genentech USA, Inc; 2015.
15. Alli [package insert]. Moon Township, PA: GlaxoSmithKline Consumer Healthcare, LP; 2015.
16. Torgerson JS, Hauptman J, Boldrin MN, et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27(1):155–61.
17. Rucker D, Padwal R, Li SK, et al. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 2007;335(7631):1194–9.

18. Kushner RF. Weight loss strategies for treatment of obesity. Prog Cardiovasc Dis 2014;56(4):465–72.
19. Qsymia [package insert]. Mountain View, CA: VIVUS, Inc; 2012.
20. Qsymia risk evaluation and mitigation strategy (REMS). VIVUS, Inc. Available at: http://www.qsymiarems.com/. Accessed February 20, 2017.
21. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012;20(2):330–42.
22. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo controlled, phase 3 trial. Lancet 2011;377(9774):1341–52.
23. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95(2):297–308.
24. A study to evaluate the effect of long-term treatment with BELVIQ (Lorcaserin HCl) on the incidence of major adverse cardiovascular events and conversion to type 2 diabetes mellitus in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors (CAMELLIATIMI). Available at: https://clinicaltrials.gov/ct2/show/NCT02019264.
25. Belviq [package insert]. Zofingen, Switzerland: Arena Pharmaceuticals; 2012.
26. Belviq XR [package insert]. Zofingen, Switzerland: Arena Pharmaceuticals; 2016.
27. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010;363(3):245–56.
28. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20(7):1426–36.
29. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011;96(10):3067–77.
30. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. Obesity (Silver Spring) 2009;17(1):30–9.
31. Contrave [package insert]. La Jolla, CA: Orexigen Therapeutics, Inc; 2016.
32. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376(9741):595–605.
33. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring) 2013;21(5):935–43.
34. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring) 2011;19(1):110–20.
35. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013;36(12):4022–9.

36. Van Can J, Sloth B, Jensen CB, et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond) 2014;38(6):784–93.
37. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. JAMA 2015;314(7):687–99.
38. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373(1):11–22.
39. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37(11):1443–51.
40. Smith SR, Garvey WT, Greenway FL, et al. Coadministration of lorcaserin and phentermine for weight management: a 12-week, randomized, pilot safety study. Obesity (Silver Spring) 2017;25(5):857–65.
41. Hollander P, Bays HE, Rosenstock J, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. Diabetes Care 2017;40(5):632–9.
42. Stanford FC, Alfaris N, Gomez G, et al. The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: a multi-center study. Surg Obes Relat Dis 2017;13(3):491–500.
43. Contrave [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2014.
44. Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk; 2014.