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Obesity: When to consider medication

These 4 cases illustrate how weight loss drugs—including the 4 newest—can be integrated into a treatment plan that includes diet, exercise, and behavior modification.

PRACTICE RECOMMENDATIONS

For patients with a body mass index (BMI) ≥ 30 kg/m² or BMI ≥ 27 kg/m² with weight-related comorbidities:

› Consider antiobesity pharmacotherapy when diet, exercise, and behavior modification do not produce sufficient weight loss. **A**

› Continue an antiobesity medication if it is deemed effective and well tolerated. **A**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

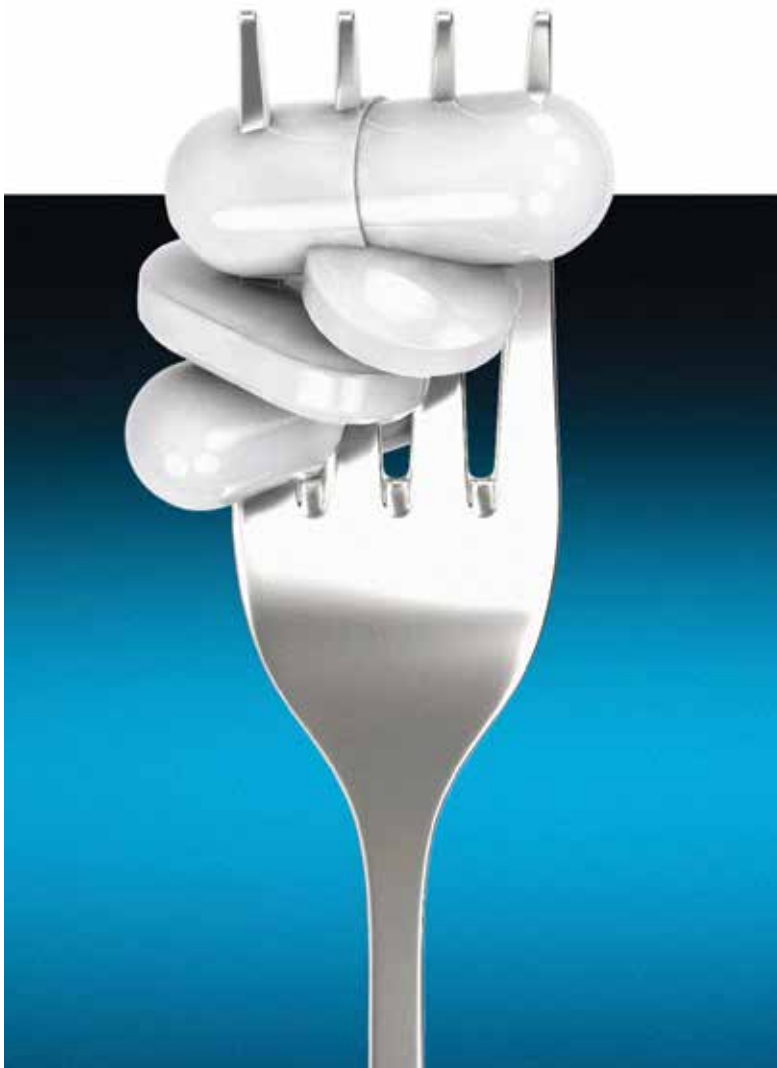
Modest weight loss of 5% to 10% among patients who are overweight or obese can result in a clinically relevant reduction in cardiovascular (CV) disease risk.¹ This amount of weight loss can increase insulin sensitivity in adipose tissue, liver, and muscle, and have a positive impact on blood sugar, blood pressure, triglycerides, and high-density lipoprotein cholesterol.^{1,2}

All patients who are obese or overweight with increased CV risk should be counseled on diet, exercise, and other behavioral interventions.³ Weight loss secondary to lifestyle modification alone, however, leads to adaptive physiologic responses, which increase appetite and reduce energy expenditure.⁴⁻⁶

Pharmacotherapy can counteract this metabolic adaptation and lead to sustained weight loss. Antiobesity medication can be considered if a patient has a body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² with obesity-related comorbidities such as hypertension, type 2 diabetes, dyslipidemia, or obstructive sleep apnea.^{3,7}

Until recently, there were few pharmacologic options approved by the US Food and Drug Administration (FDA) for the management of obesity. The mainstays of treatment were phentermine (Adipex-P, Ionamin, Suprenza) and orlistat (Alli, Xenical). Since 2012, however, 4 agents have been approved as adjuncts to a reduced-calorie diet and increased physical activity for long-term weight management.^{8,9} Phentermine/topiramate extended-release (ER) (Qsymia) and lorcaserin (Belviq) were approved in 2012,^{10,11} and naltrexone sustained release (SR)/bupropion SR (Contrave) and liraglutide 3 mg (Saxenda) were approved in 2014.^{12,13} (TABLE^{9,14-39}). These medications have the potential to not only limit weight gain, but also promote weight loss and, thus, improve blood pressure, cholesterol, glucose, and insulin.⁴⁰

Despite the growing obesity epidemic and the availability of several additional medications for chronic weight manage-



Weight loss secondary to lifestyle changes can lead to adaptive physiologic responses, which increase appetite and reduce energy expenditure. Pharmacotherapy can counteract this.

ment, use of antiobesity pharmacotherapy has been limited. Barriers to use include inadequate training of health care professionals, poor insurance coverage for new agents, and low reimbursement for office visits to address weight.⁴¹

In addition, the number of obesity medicine specialists, while increasing, is still not sufficient. Therefore, it is imperative for other health care professionals—namely family practitioners—to be aware of the treatment options available to patients who are overweight or obese and to be adept at using them.

In this review, we present 4 cases that depict patients who could benefit from the addition of antiobesity pharmacotherapy to a comprehensive treatment plan that includes diet, physical activity, and behavioral modification.

CASE 1 ▶ Melissa C, a 27-year-old woman with obesity (BMI 33 kg/m²), hyperlipidemia,

and migraine headaches, presents for weight management. Despite a calorie-reduced diet and 200 minutes per week of exercise for the past 6 months, she has been unable to lose weight. The only medications she's taking are oral contraceptive pills and sumatriptan, as needed. She suffers from migraines 3 times a month and has no anxiety. Laboratory test results are normal with the exception of an elevated low-density lipoprotein (LDL) level.

Which medication is an appropriate next step for Ms. C?

Discussion

When considering an antiobesity agent for any patient, there are 2 important questions to ask:

- Are there contraindications, drug-drug interactions, or undesirable adverse effects associated with this medication that could be problematic for the patient?
- Can this medication improve other



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How confident are you when it comes to prescribing medications for obesity?

- Extremely confident
- Somewhat confident
- Not confident at all

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TABLE

Antiobesity medications: What to expect and who makes a good candidate^{9,14-39}

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects	Good candidates	Poor candidates
Phentermine (Adipex-P, ¹⁵ Ionamin, ¹⁶ Lomaira, ¹⁷ Suprenza ¹⁸) Schedule IV controlled substance NOTE: Approved for short-term use	Adrenergic agonist 8-37.5 mg/d Capsule, tablet	Aronne LJ, et al ¹⁹ 28 weeks	15 mg/d 7.5 mg/d Placebo (topiramate ER and phentermine/topiramate ER arms excluded)	6.06* 5.45* 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 (Alli, ²⁰ Xenical ²¹)	Lipase inhibitor 60-120 mg tid with meals Capsule	XENDOS ²² 208 weeks	120 mg tid Placebo	9.6 (Week 52)* 5.25 (Week 208)* 5.61 (Week 52) 2.71 (Week 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
Phentermine/topiramate ER (Qsymia) ²³ Schedule IV controlled substance	Adrenergic agonist/neurostabilizer 3.75/23-15/92 mg/d Capsule	EQUIP ²⁴ 56 weeks CONQUER ²⁵ 56 weeks SEQUEL ²⁶ 108 weeks (52-week extension of CONQUER trial)	15/92 mg/d 3.75/23 mg/d Placebo 15/92 mg/d 7.5/46 mg/d Placebo 15/92 mg/d 7.5/46 mg/d Placebo	10.9* 5.1* 1.6 9.8* 7.8* 1.2 10.5* 9.3* 1.8 (Weeks 0-108)	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

symptoms or conditions the patient has?

In addition, see “Before prescribing anti-obesity medication . . .” page 613.

■ **Phentermine/topiramate ER** is a good first choice for this young patient with class I (BMI 30-34.9 kg/m²) obesity and migraines, as she can likely tolerate a stimulant and her migraines might improve with topiramate.

Before starting the medication, ask about insomnia and nephrolithiasis in addition to anxiety and other contraindications (ie, glaucoma, hyperthyroidism, recent monoamine oxidase inhibitor use, or a known hypersensitivity or idiosyncrasy to sympathomimetic amines).²³ The most common adverse events reported in phase III trials were dry mouth, paresthesia, and constipation.²⁴⁻²⁶

TABLE

Antiobesity medications: What to expect and who makes a good candidate^{9,14-39}
continued

Medication	Mechanism, dosage, and available formulations	Trial and duration	Trial arms	Weight loss (%)	Most common adverse effects	Good candidates	Poor candidates
Lorcaserin (Belviq, Belviq XR) ²⁷ Schedule IV controlled substance	Serotonin 5-HT _{2C} receptor agonist 10 mg bid or 20 mg/d ER Tablet	BLOOM ²⁸ 52 weeks	10 mg bid Placebo	5.8* 2.2	Headache, dizziness, fatigue, nausea, dry mouth, constipation	Patients who report inadequate meal satiety	Patients on other serotonin modulating medications; patients with known cardiac valvular disease; patients who are pregnant
		BLOSSOM ²⁹ 52 weeks	10 mg bid 10 mg/d Placebo	5.8* 4.7* 2.8			
			BLOOM-DM ³⁰ 52 weeks	10 mg bid 10 mg/d Placebo			
		Naltrexone SR-/bupropion SR (Contrave) ³¹		Opioid receptor antagonist-/dopamine and norepinephrine reuptake inhibitor 8/90 mg/d-16/180 mg bid Tablet			
COR-II ³³ 56 weeks	16/180 mg bid Placebo		6.4* 1.2				
	COR-BMOD ³⁴ 56 weeks		16/180 mg bid Placebo		9.3* 5.1		
COR-DIABETES ³⁵ 56 weeks			16/180 mg bid Placebo		5.0* 1.8		
Liraglutide 3 mg (Saxenda) ³⁶	GLP-1 receptor agonist 0.6-3 mg/d Prefilled pen for subcutaneous injection	SCALE Obesity and Pre-diabetes ³⁷ 56 weeks	3 mg/d Placebo	8.0* 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 an aversion to needles, history of pancreatitis, personal or family history of medullary thyroid carcinoma, or multiple endocrine neoplasia syndrome type 2; patients who are pregnant
		SCALE Diabetes ³⁸ 56 weeks	3 mg/d 1.8 mg/d Placebo	6* 4.7* 2			
			SCALE Maintenance ³⁹ 56 weeks (after initial ≥5% weight loss with LCD)	3 mg/d Placebo			

ER, extended release; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; LCD, low-calorie diet; MAOI, monoamine oxidase inhibitor; XR, extended release.
*P<.001 vs placebo.

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■ **Not for pregnant women.** Women of childbearing age must have a negative pregnancy test before starting phentermine/topiramate ER and every month while taking the medication. The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) to inform prescribers and patients about the increased risk of congenital malformation, specifically orofacial clefts, in infants exposed to topiramate during the first trimester of pregnancy.⁴² REMS focuses on the importance of pregnancy prevention, the consistent use of birth control, and the need to discontinue phentermine/topiramate ER immediately if pregnancy occurs.

■ **Flexible dosing.** Phentermine/topiramate ER is available in 4 dosages: phentermine 3.75 mg/topiramate 23 mg ER; phentermine 7.5 mg/topiramate 46 mg ER; phentermine 11.25 mg/topiramate 69 mg ER; and phentermine 15 mg/topiramate 92 mg ER. Gradual dose escalation minimizes risks and adverse events.²³

Monitor patients frequently to evaluate for adverse effects and ensure adherence to diet, exercise, and lifestyle modifications. If weight loss is slower or less robust than expected, check for dietary indiscretion, as medications have limited efficacy without appropriate behavioral changes.

■ **Discontinue phentermine/topiramate ER** if the patient does not achieve 5% weight loss after 12 weeks on the maximum dose, as it is unlikely that she will achieve and sustain clinically meaningful weight loss with continued treatment.²³ In this case, consider another agent with a different mechanism of action. Any of the other antiobesity medications could be appropriate for this patient.

CASE 2 ▶ Norman S, a 52-year-old overweight man (BMI 29 kg/m²) with type 2 diabetes, hyperlipidemia, osteoarthritis, and glaucoma, has recently hit a plateau with his weight loss. He lost 45 pounds secondary to diet and exercise, but hasn't been able to lose any more. He also struggles with constant hunger. His medications include metformin 1000 mg bid, atorvastatin 10 mg/d, and occasional acetaminophen/oxycodone for knee pain until he undergoes a left knee replacement. Labora-

tory values are normal except for a hemoglobin A1c of 7.2%.

Mr. S is afraid of needles and cannot tolerate stimulants due to anxiety. Which medication is an appropriate next step for this patient?

Discussion

Lorcaserin is a good choice for this patient who is overweight and has several weight-related comorbidities. He has worked hard to lose a significant number of pounds, and is now at high risk of regaining them. That's because his appetite has increased with his new exercise regimen, but his energy expenditure has decreased secondary to metabolic adaptation.

■ **Narrowing the field.** Naltrexone SR/bupropion SR cannot be used because of his opioid use. Phentermine/topiramate ER is contraindicated for patients with glaucoma, and liraglutide 3 mg is not appropriate given the patient's fear of needles.

He could try orlistat, especially if he struggles with constipation, but the gastrointestinal adverse effects are difficult for many patients to tolerate. While not an antiobesity medication, a sodium-glucose co-transporter 2 (SGLT2) inhibitor could be prescribed for his diabetes and may also promote weight loss.⁴³

■ **An appealing choice.** The glucose-lowering effect of lorcaserin could provide an added benefit for the patient. The BLOOM-DM (Behavioral modification and lorcaserin for overweight and obesity management in diabetes mellitus) study reported a mean reduction in hemoglobin A1c of 0.9% in the treatment group compared with a 0.4% reduction in the placebo group,³⁰ and the effect of lorcaserin on A1c appeared to be independent of weight loss.

■ **Mechanism of action: Cause for concern?** Although lorcaserin selectively binds to serotonin 5-HT_{2C} receptors, the theoretical risk of cardiac valvulopathy was evaluated in phase III studies, as fenfluramine, a 5-HT_{2B}-receptor agonist, was withdrawn from the US market in 1997 for this reason.⁴⁴ Both the BLOOM (Behavioral modification and lorcaserin for overweight and obesity management) and BLOSSOM (Behavioral

modification and lorcaserin second study for obesity management) studies found that lorcaserin did not increase the incidence of FDA-defined cardiac valvulopathy.^{28,29}

Formulations/adverse effects. Lorcaserin is available in 2 formulations: 10-mg tablets, which are taken twice daily, or 20-mg XR tablets, which are taken once daily. Both are generally well tolerated.^{27,45} The most common adverse event reported in phase III trials was headache.^{28,30,43} Discontinue lorcaserin if the patient does not lose 5% of his initial weight after 12 weeks, as weight loss at this stage is a good predictor of longer-term success.⁴⁶

Some patients don't respond. Interestingly, a subset of patients do not respond to lorcaserin. The most likely explanation for different responses to the medication is that there are many causes of obesity, only some of which respond to 5-HT_{2C} agonism. Currently, we do not perform pharmacogenomic testing before prescribing lorcaserin, but perhaps an inexpensive test to identify responders will be available in the future.

CASE 3 ▶ Kathryn M, a 38-year-old woman with obesity (BMI 42 kg/m²), obstructive sleep apnea, gastroesophageal reflux disease, and depression, is eager to get better control over her weight. Her medications include lansoprazole 30 mg/d and a multivitamin. She reports constantly thinking about food and not being able to control her impulses to buy large quantities of unhealthy snacks. She is so preoccupied by thoughts of food that she has difficulty concentrating at work.

Ms. M smokes a quarter of a pack of cigarettes daily, but she is ready to quit. She views bariatric surgery as a "last resort" and has no anxiety, pain, or history of seizures. Which medication is appropriate for this patient?

Discussion

This patient with class III obesity (BMI ≥40 kg/m²) is eligible for bariatric surgery; however, she is not interested in pursuing it at this time. It is important to discuss all of her options before deciding on a treatment plan. For patients like Ms. M, who would benefit from more than modest weight loss, con-

Before prescribing antiobesity medication . . .

Have a frank discussion with the patient and be sure to cover the following points:

1. The rationale for pharmacologic treatment is to counteract adaptive physiologic responses, which increase appetite and reduce energy expenditure, in response to diet-induced weight loss.
2. Antiobesity medication is only one component of a comprehensive treatment plan, which also includes diet, physical activity, and behavior modification.
3. Antiobesity agents are intended for long-term use, as obesity is a chronic disease. If/when you stop the medication, there may be some weight regain, similar to an increase in blood pressure after discontinuing an antihypertensive agent.
4. Because antiobesity medications improve many parameters including glucose/hemoglobin A1c, lipids, blood pressure, and waist circumference, it is possible that the addition of one antiobesity medication can reduce, or even eliminate, the need for several other medications.

Remember that many patients who present for obesity management have experienced weight bias. It is important to not be judgmental, but rather explain why obesity is a chronic disease. If patients understand the physiology of their condition, they will understand that their limited success with weight loss in the past is not just a matter of willpower. Lifestyle change and weight loss are extremely difficult, so it is important to provide encouragement and support for ongoing behavioral modification.

sider a multidisciplinary approach including lifestyle modifications, pharmacotherapy, devices (eg, an intragastric balloon), and/or surgery. You would need to make clear to Ms. M that she may still be eligible for insurance coverage for surgery if she changes her mind after pursuing other treatments as long as her BMI remains ≥35 kg/m² with obesity-related comorbidities.

Naltrexone SR/bupropion SR is a good choice for Ms. M because she describes debilitating cravings and addictive behavior surrounding food. Patients taking naltrexone SR/bupropion SR in the Contrave Obesity Research (COR)-I and COR-II phase III trials experienced a reduced frequency of food cravings, reduced difficulty in resisting food cravings, and an increased ability to control eating compared with those assigned to placebo.^{32,33}

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➤ **Naltrexone SR/bupropion SR is a good choice for patients who describe debilitating cravings and addictive behavior surrounding food.**

■ **Added benefits.** Bupropion could also help Ms. M quit smoking and improve her mood, as it is FDA-approved for smoking cessation and depression. She denies anxiety and seizures, so bupropion is not contraindicated. Even if a patient denies a history of seizure, ask about any conditions that predispose to seizures, such as anorexia nervosa or bulimia or the abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.

■ **Opioid use.** Although the patient denies pain, ask about potential opioid use, as naltrexone is an opioid receptor antagonist. Patients should be informed that opioids may be ineffective if they are required unexpectedly (eg, for trauma) and that naltrexone SR/bupropion SR should be withheld for any planned surgical procedure potentially requiring opioid use.

■ **Other options.** While naltrexone SR/bupropion SR is the most appropriate choice for this patient because it addresses Ms. M's problematic eating behaviors while potentially improving mood and assisting with smoking cessation, phentermine/topiramate ER, lorcaserin, and liraglutide 3 mg could also be used and should certainly be tried if naltrexone SR/bupropion SR does not produce the desired weight loss.

■ **Adverse effects.** Titrate naltrexone SR/bupropion SR slowly to the treatment dose to minimize risks and adverse events.³¹ The most common adverse effects reported in phase III trials were nausea, constipation, and headache.^{34,35,45,46} Discontinue naltrexone SR/bupropion SR if the patient does not achieve 5% weight loss at 16 weeks (after 12 weeks at the maintenance dose).³¹

CASE 4 ▶ William P, a 65-year-old man with obesity (BMI 39 kg/m²) who underwent Roux-en-Y gastric bypass surgery and who has type 2 diabetes, congestive heart failure, coronary artery disease, hypertension, and hyperlipidemia, remains concerned about his weight. He lost 100 lbs following surgery and maintained his weight for 3 years, but then regained 30 lbs. He comes in for an office visit because he's concerned about his increasing blood sugar and wants to prevent further weight

gain. His medications include metformin 1000 mg bid, lisinopril 5 mg/d, carvedilol 12.5 mg bid, simvastatin 20 mg/d, and aspirin 81 mg/d. Laboratory test results are normal except for a hemoglobin A1c of 8%. He denies pancreatitis and a personal or family history of thyroid cancer.

Which medication is an appropriate next step for Mr. P?

Discussion

Pharmacotherapy is a great option for this patient, who is regaining weight following bariatric surgery. Phentermine/topiramate ER is the only medication that would be contraindicated because of his heart disease. Lorcaserin and naltrexone SR/bupropion SR could be considered, but liraglutide 3 mg is the most appropriate option, given his need for further glucose control.

Furthermore, the recent LEADER (Liraglutide effect and action in diabetes: evaluation of CV outcome results) trial reported a significant mortality benefit with liraglutide 1.8 mg/d among patients with type 2 diabetes and high CV risk.⁴⁷ The study found that liraglutide was superior to placebo in reducing CV events.

■ **Contraindications.** Ask patients about a history of pancreatitis before starting liraglutide 3 mg given the possible increased risk. In addition, liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Thyroid C-cell tumors have been found in rodents given supratherapeutic doses of liraglutide;⁴⁸ however, there is no evidence of liraglutide causing C-cell tumors in humans.

For patients taking a medication that can cause hypoglycemia, such as insulin or a sulfonylurea, monitor blood sugar and consider reducing the dose of that medication when starting liraglutide.

■ **Administration and titration.** Liraglutide is injected subcutaneously once daily. The dose is titrated up weekly to reduce gastrointestinal symptoms.³⁶ The most common adverse effects reported in phase III trials were nausea, diarrhea, and constipation.³⁷⁻³⁹ Discontinue liraglutide 3 mg if the patient

does not lose at least 4% of baseline body weight after 16 weeks.⁴⁹

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