CME CREDIT

LEARNING OBJECTIVE: Readers will prescribe and monitor pharmacotherapy as indicated to help patients lose weight

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Pharmacotherapy for obesity: What you need to know

ABSTRACT

Weight-loss drugs are being evaluated for their role in obesity management. This article reviews the available weight-loss drugs, their efficacy and side effects, and their best clinical use.

KEY POINTS

Weight-loss drugs should only be used in combination with lifestyle modification.

Preparations that combine 2 drugs have greater weight-loss benefits and better side-effect profiles.

Weight-loss drugs should be discontinued if substantial (5%) weight loss has not occurred by 12 weeks.

All weight-loss drugs are contraindicated in pregnancy.

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WEIGHT-LOSS DRUGS are not magic pills, but they can help patients lose about 10 to 25 more pounds than they otherwise could, when used in a program that includes diet, exercise, and other lifestyle changes.

This article reviews current drug therapy for obesity, including dosages, approved duration of use, mechanisms of action, adverse effects, potential interactions, contraindications, and data on efficacy. **Table 1** summarizes the drugs currently approved by the US Food and Drug Administration (FDA) for this indication.

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HALF OF ADULTS MAY BE OBESE BY 2030

Obesity is a major public health challenge in the United States, with nearly 37% of adults classified as obese.[1] The prevalence has increased more than 75% since 1980,[2] and it is estimated that 51% of US adults will be obese by 2030.[3] Obesity is the second-leading cause of preventable deaths, after smoking.[4]

Obesity increases the risk of many chronic medical conditions, including type 2 diabetes mellitus, heart disease, hypertension, stroke, nonalcoholic fatty liver disease, osteoarthritis, and cancers of the breast, colon, endometrium, and kidney.[5]

WHEN IS DRUG THERAPY INDICATED?

Guidelines from the major obesity societies recommend that all weight-loss programs have a lifestyle component that includes a low-calorie diet, increased physical activity, and behavioral therapy, to which pharmacotherapy may be added as an adjunct.[6–8]

TABLE 1

Drugs approved by the US Food and Drug Administration for treating obesity[a]

Drug	Mechanism of action	Contraindications and warnings	Serious interactions	Adverse reactions	Dosage and monitoring	Cost[b]
Phentermine	Suppresses appetite	**Contraindications** Hyperthyroidism Glaucoma Agitation Pregnancy or breastfeeding (category X) MAO inhibitor within 14 days **Use with caution** Cardiovascular disease History of drug abuse	Monoamine oxidase (MAO) inhibitors	Nervousness Insomnia Dry mouth	15, 30, or 37.5 mg daily before breakfast or 1–2 hours after Schedule IV	$12
Orlistat	Inhibits fat absorption	**Contraindications** Pregnancy or breastfeeding (category X)	Cyclosporine Warfarin Other fat-soluble drugs (see text)	Gastrointestinal: abdominal pain, bowel urgency, steatorrhea, fecal incontinence Hepatotoxicity Oxalate nephropathy	60 or 120 mg 3 times a day during or within 1 hour of a fat-containing meal Monitor renal function	$530
Phentermine-topiramate[c]	Phentermine: see above Topiramate: unknown	**Contraindications** Hyperthyroidism Glaucoma Agitation Pregnancy or breastfeeding (category X) MAO inhibitor within 14 days **Use with caution** Cardiovascular disease History of drug abuse Depression	MAO inhibitors Opioid or other central nervous system depressants CYP3A4 and CYP1A2 inducers	Dry mouth Dizziness Constipation Paresthesia Psychiatric and cognitive adverse events Nephrolithiasis Increased heart rate Angle-closure glaucoma Acute myopia	3.75/23 mg daily for 14 days, then 7.5/46 mg daily If < 3% weight loss at 12 weeks, increase to 11.25/69 mg daily for 14 days, followed by 15/92 mg daily thereafter Gradually discontinue if < 5% weight loss at 12 weeks on highest dose Pregnancy test at baseline and monthly for women of childbearing age Schedule IV Adjust for renal impairment	$199
Lorcaserin	Suppresses appetite	**Contraindications** Creatinine clearance < 30 mL/min Pregnancy (category X) **Use with caution** Creatinine clearance 30–50 mL/min Severe hepatic impairment	Serotonergic agents	Dry mouth Dizziness Somnolence Headache Gastrointestinal disturbance	10 mg twice a day Discontinue if < 5% weight loss at 12 weeks Monitor blood glucose level closely in patients with diabetes mellitus because of risk of hypoglycemia Schedule IV	$212
Naltrexone-bupropion	Suppresses appetite	**Contraindications** End-stage renal disease Pregnancy or breastfeeding (category X) MAO inhibitor within 14 days Uncontrolled hypertension Seizure disorder Eating disorder	Bupropion Chronic opioid use or acute opiate withdrawal Linezolid CYP2B6 inhibitors	Nausea, vomiting Constipation or diarrhea Headache Dizziness Insomnia Dry mouth	8/90 mg for 7 days; then twice a day for 7 days; then 2 tablets in morning and 1 tablet in the evening for 7 days, followed by 2 tablets twice a day thereafter Discontinue if < 5% weight loss at 12 weeks Adjust for renal and hepatic impairment	$212
Liraglutide	Slows gastric emptying, increases satiety	**Contraindications** Personal or family history of medullary thyroid cancer (multiple endocrine neoplasia type 2 syndrome) Pregnancy or breastfeeding (category X) Moderate to severe renal impairment **Use with caution** History of pancreatitis Severe renal insufficiency	Other hypoglycemic agents	Nausea, vomiting Diarrhea, constipation Hypoglycemia Pancreatitis Gallbladder disease Renal impairment Suicidal thoughts	0.6 mg subcutaneously daily, increase by 0.6 mg weekly to a daily target dose of 3 mg Discontinue if < 4% weight loss at 16 weeks	$1,095

[a] In various trials, these drugs led to weight loss of 5.0 to 12.9 kg compared with placebo.

[b] Average wholesale cost for 1 month, per Healthcare Bluebook. https://healthcarebluebook.com/page_ConsumerFront.aspx.

[c] Prescribers must complete Healthcare Provider Training Program and HCP Registration Form before they can prescribe this medication; see www.qsymiarems.com/.

TABLE 2

Treatments by body mass index and comorbidity

Body mass index (kg/m²)	Lifestyle modification	Pharmacotherapy	Bariatric surgery
25–29.9	X		
30–39.0 or 27–34.9 with comorbidities	X	X	
≥ 40 or ≥ 35 with comorbidities	X	X	X

Weight-loss medications are indicated for patients who have a body mass index (BMI) of at least 30 kg/m^2 or who have obesity-associated comorbidities and a BMI of at least 27 kg/m^2. However, the best results are achieved when pharmacotherapy is combined with lifestyle modification.[9]

Weight-loss surgery is a safe and effective option for patients with a BMI of at least 40 kg/m^2 or, with comorbidities, a BMI of at least 35 kg/m^2 (**Table 2**). About 15 million Americans have a BMI of at least 40 kg/m^2. Although bariatric surgery is the most efficient and longest-lasting treatment, only 1% of the eligible population receives surgical treatment.[10]

HISTORY OF WEIGHT-LOSS DRUGS: NOT A PRETTY PICTURE

The earliest drugs to induce weight loss, which worked mainly by increasing metabolism, included thyroid hormone, amphetamines (which also suppress appetite), and dinitrophenol (a pesticide). Adverse reactions limited their usefulness: cardiovascular effects with thyroid hormones, abuse potential with amphetamines, and neuropathy and cataracts with dinitrophenol.

Researchers then looked to drugs that could suppress appetite like amphetamines do, but without the potential for abuse. Medications that increased levels of norepinephrine and serotonin, both by increasing release and decreasing reuptake of these neuromodulators, had some success. But again, serious adverse effects occurred, and several drugs had to be withdrawn from the market.

The most publicized of these withdrawals was for the combination fenfluramine and phentermine ("fen-phen") and its cousin dexfenfluramine (Redux). Up to 30% of patients taking fenfluramine-phentermine developed echocardiographic evidence of valvular heart disease.[11] Fenfluramine also increased the risk of pulmonary hypertension. These findings led to the 1997 withdrawal of these drugs from the US market.

Sibutramine (Meridia), a norepinephrine and serotonin reuptake inhibitor, was approved for weight loss in 1997. Increases in blood pressure and heart rate were noted in the initial trial,[12] and then a postmarketing study found increased rates of nonfatal myocardial infarction and stroke in patients with preexisting cardiovascular disease or diabetes mellitus.[13] Based on these results, sibutramine was withdrawn from both US and European markets.

Rimonabant (Acomplia, Zimulti), a cannabinoid-receptor inhibitor, was approved in Europe in 2006, but its approval was withdrawn just 2 years later because of increased suicidality in a postmarketing study.[14] It was never approved for use in the United States.

Weight-loss drugs are indicated for those with BMI ≥ 30 kg/m² or with BMI ≥ 27 kg/m² and obesity-associated comorbidities

NORADRENERGIC SYMPATHOMIMETICS: FOR SHORT-TERM USE

Several noradrenergic sympathomimetic drugs are FDA-approved for short-term weight loss, but phentermine is by far the most commonly prescribed drug in this class. In fact, it is the most commonly prescribed drug for obesity in the United States.[15]

Phentermine

Phentermine is an atypical amphetamine analogue that suppresses appetite by norepinephrine agonism in the central nervous system.

The FDA approved it for short-term weight management in 1959, and its use became widespread in the 1960s, followed by decades of popularity.

Dosage. Phentermine is prescribed at an oral dose of 15, 30, or 37.5 mg daily, either before breakfast or 1 to 2 hours after. It is a schedule IV controlled substance, based on its similarity to amphetamine. (The 5 US controlled substance schedules range from schedule I, which includes heroin, amphetamine, and cannabis, to schedule V, which includes cough syrups containing no more than 200 mg of codeine per 100 mL.) However, concerns about addiction and dependence with phentermine are largely unfounded, and abrupt cessation of the drug has not been shown to cause amphetamine-like withdrawal.[16]

Adverse effects. Common adverse reactions include nervousness, insomnia, and dry mouth, but these effects tend to wane with continued use.

Contraindications. Cardiovascular disease is a contraindication to phentermine because of concerns about increased blood pressure and pulse rate, although these concerns seem to be more theoretic than observed.[16] Other contraindications include hyperthyroidism, glaucoma, agitation, a history of drug abuse, pregnancy, breastfeeding, and current or recent use of a monoamine oxidase inhibitor. No serious adverse events have been reported in trials of phentermine.

Efficacy. In a pooled analysis of 6 trials lasting 2 to 24 weeks completed between 1975 and 1999, phentermine-treated patients lost an average of 3.6 kg more weight than placebo recipients.[17] More than 80% of study participants were women.

In a 36-week study in 108 women,[18] participants lost a mean of 12.2 kg with continuous phentermine use, 13.0 kg with intermittent use (4 weeks on, 4 weeks off; the difference was not significant), and 4.8 kg with placebo.

Minimal data exist on long-term efficacy of phentermine monotherapy.

About 15 million Americans have a BMI ≥ 40 kg/m²

DRUGS FOR LONG-TERM THERAPY

Orlistat

Orlistat was approved as a prescription drug (Xenical, 120 mg) in 1999 and as an over-the-counter medication (Alli, 60 mg) in 2007.

Orlistat works by inhibiting pancreatic and gastric lipase, causing incomplete hydrolysis of ingested fat, thereby increasing fecal fat excretion in a dose-dependent manner. It is a good choice for weight-loss drug therapy because of its safe cardiovascular risk profile and beneficial effects on lipid levels. However, its long-term effect on weight is only modest.[19,20]

Dosage. The dosage for prescription orlistat is 120 mg 3 times per day, in addition to a low-fat diet (< 30% of daily calories from fat). To prevent potential deficiencies of fat-soluble vitamins, a daily multivitamin supplement is recommended, but it should not be taken with meals.

Efficacy. In a 2014 systematic review, 35% to 73% of patients treated with orlistat 120 mg had lost at least 5% of their body weight at 1 year, and 14% to 41% had lost at least 10%.[21] At the end of the second year, orlistat-treated patients had lost about 3.3 kg more than placebo recipients.

In a randomized trial,[22] 4 years of treatment with orlistat vs placebo led to a significant (37.3%) risk reduction in the incidence of type 2 diabetes mellitus in obese participants, as well as significant improvements in cardiovascular risk factors. Mean weight loss at 1 year was significantly greater with orlistat than with placebo (10.6 vs 6.2 kg), and it remained greater at 4 years (5.8 vs 3.0 kg; $P < .001$).

Adverse effects. Long-term orlistat use is hampered by adverse reactions. A population-based, retrospective cohort analysis showed that fewer than 10% of patients were still using it at 1 year, and only 2% were using it at 2 years, although reasons for discontinuation were not reported.[23]

Adverse reactions are predominantly gastrointestinal, attributed to the high content of undigested fat in stools. Patients who do not limit their dietary fat intake are affected the most. Other reported adverse reactions include hepatotoxicity and oxalate-induced nephropathy.

Orlistat has been reported to interfere with some drugs, particularly those that are lipophilic. Drugs that should be closely monitored with orlistat are warfarin, amiodarone, cyclosporine, certain antiepileptic drugs, and levothyroxine.

Phentermine-topiramate

The combination of phentermine and topiramate was approved by the FDA in 2012 and is available under the brand name Qsymia.

Topiramate had been approved for treating seizure disorder in 1996 and as migraine prophylaxis in 2004. It is not approved as monotherapy for obesity; however, patients taking it for seizures or for psychiatric disorders (eg, binge eating, borderline personality disorder) have reported weight loss during treatment.

How topiramate promotes weight loss is not known. Proposed mechanisms include taste inhibition by carbonic anhydrase, influences on gamma-aminobutyric acid transmission causing appetite suppression, sensitization of insulin activity, and adiponectin secretion in the peripheral tissues.[24,25]

Phentermine-topiramate therapy has an advantage over monotherapy because lower doses of each medication can be used to achieve the same benefit, thus avoiding dose-related adverse reactions.

Dosage. Phentermine-topiramate is available in capsules containing 3.75/23, 7.5/46, 11.25/69, and 15/92 mg. The recommended starting dosage is 3.75/23 mg/day for 14 days, increasing to 7.5/46 mg/day. If patients do not lose at least 3% of their body weight after 12 weeks, the dose can be increased to 11.25/69 mg daily for 14 days, followed by 15/92 mg daily.[26] Phentermine-topiramate is a schedule IV controlled substance with a low potential for abuse and dependence.

Efficacy. Approval of phentermine-topiramate for treating obesity was primarily based on 3 clinical trials.[27–29] In 1 of these trials,[28] at 1 year, patients had lost 9.9 kg with the medium dose and 12.9 kg with the high dose.

Adverse effects. Phentermine-topiramate was well tolerated in the trials. The most commonly reported adverse reactions were dry mouth, dizziness, constipation, insomnia, dysgeusia, paresthesia, and increased resting heart rate.[28,29] Acute myopia and angle-closure glaucoma also have been reported with topiramate.[30] Topiramate monotherapy has been associated with dose-dependent neuropsychiatric adverse effects, including memory symptoms and depression. However, across all 3 trials of phentermine-topiramate therapy, symptoms of depression improved over time, and no significant increase in suicide risk was identified.[27–29]

Recommended monitoring for patients on phentermine-topiramate includes a blood chemistry panel, resting heart rate, blood pressure, and depression screening.

Because topiramate has teratogenic potential (craniofacial abnormalities), it is labeled as pregnancy category X (contraindicated). A negative pregnancy test is needed before women of childbearing age take the drug and monthly thereafter. Women should be counseled to use effective birth control. A home pregnancy test is an alternative to laboratory testing, but this option should be left to the prescribing clinician's judgment and be based on reliability of the test and patient compliance.

Lorcaserin

Lorcaserin (Belviq) was approved by the FDA in 2012 for chronic weight management. It suppresses appetite by activating the serotonin 2C receptor in the brain. Because it is selective for the 2C receptor, it does not appear to have the same detrimental effects on heart valves as occurred with less-selective serotonergic agents such as fenfluramine and dexfenfluramine.[31]

Minimal data exist on long-term efficacy of phentermine monotherapy

Dosage. The recommended dosage for lorcaserin is 10 mg twice daily. Lorcaserin is a schedule IV controlled substance because of studies that showed increases in positive subjective measures such as euphoria in patients taking the drug. The incidence of euphoria was similar to that seen with zolpidem.[32]

Efficacy. Lorcaserin was approved on the basis of 2 trials in nondiabetic obese and overweight adults who did not have diabetes but who had a weight-related condition,[33,34] and in a third trial in obese and overweight adults with type 2 diabetes mellitus who were taking oral hypoglycemic agents.[35] In these trials, lorcaserin use resulted in a modest 4.7- to 5.8-kg weight loss compared with 1.6 to 2.2 kg in the placebo group.[33–35] There was a high dropout rate in all 3 of these studies (33% to 45% of participants).

A pilot study that added phentermine to lorcaserin yielded double the weight loss from lorcaserin alone.[36] This drug combination warrants further investigation.

Contraindications. Lorcaserin should not be given to patients who have severe renal insufficiency (creatinine clearance < 30 mL/min) or severe hepatic impairment, or who are pregnant.

Adverse effects. Common adverse reactions include dry mouth, dizziness, somnolence, headache, and gastrointestinal disturbances (nausea, constipation, or diarrhea).[37]

Patients with type 2 diabetes mellitus should be monitored for hypoglycemia.

Lorcaserin should be used with extreme caution in patients taking other serotonergic agents because of the risk of the serotonin syndrome.

A theoretic potential for increased risk of breast cancer also exists with lorcaserin. When rats were given supraphysiologic doses of lorcaserin (more than 50 times higher than recommended in humans), fibroadenomas and adenocarcinomas occurred at higher rates.[38] Breast cancer data were not reported in the 3 randomized trials discussed above.[33–35]

Naltrexone-bupropion

Adverse effects of orlistat are mostly gastrointestinal

The combination of naltrexone and bupropion was approved by the FDA in 2014 under the brand name Contrave. Both drugs are approved for monotherapy in conditions other than obesity.

Naltrexone is a mu opioid receptor antagonist approved to treat alcohol and opioid dependency. Bupropion is a dopamine-norepinephrine reuptake inhibitor approved to treat depression and to help with smoking cessation. Combining the drugs produces weight loss and metabolic benefits through effects on 2 areas of the brain that regulate food intake: the hypothalamus (appetite) and the mesolimbic dopamine circuit (reward system).

Dosage. Naltrexone-bupropion comes as an extended-release tablet of 8/90 mg. The maintenance dose of 2 tablets twice daily is reached at week 4 through a specific dose-titration regimen (**Table 1**). The dose should be adjusted if patients have renal or hepatic impairment or if they are also taking a CYP2B6 inhibitor.

Efficacy. FDA approval was based on the results of 4 clinical trials.[39–42] Using a modified intention-to-treat analysis, Yanovski and Yanovski[43] calculated that at 1 year, placebo-subtracted mean weight loss was 4.6% (4.9 kg), and mean total weight loss was 6.8% (7.3 kg) across the studies. Attrition rates, however, were high, ranging from 42% to 50%.

Cardiometabolic effects in 2 of the trials[40,41] included decreased waist circumference, triglyceride levels, and C-reactive protein levels, and increased high-density lipoprotein levels at the initial dose. At the maintenance dose, additional lowering of fasting plasma insulin and glucose levels occurred along with lower levels of the homeostatic model assessment of insulin resistance. In the COR-Diabetes Study Group trial, patients with type 2 diabetes mellitus had decreased hemoglobin A_{1c} levels without an increase in hypoglycemia and an increased likelihood of reaching the target hemoglobin A_{1c} level below 7%.[39]

Contraindications. Naltrexone-bupropion is contraindicated for patients who have uncontrolled hypertension, seizure disorder, eating disorder, or end-stage renal failure; who are pregnant; or who have been treated with a monoamine oxidase inhibitor within 14 days. It should not be used with other bupropion-containing products or in patients who have taken opioids chronically or have acute opiate withdrawal.

Because of its bupropion component, this product carries an FDA black-box warning about possible suicidal thoughts and behaviors and neuropsychiatric reactions.

Adverse effects. The adverse reactions most commonly associated with naltrexone-bupropion were nausea (32.5%), constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%).[44]

Liraglutide

Liraglutide, previously FDA-approved to treat type 2 diabetes mellitus under the brand name Victoza, received approval in 2014 in a higher-dose formulation (Saxenda) to treat obesity.

Liraglutide is a glucagon-like peptide-1 receptor agonist that stimulates glucose-dependent insulin release from the pancreatic islet cells, slows gastric emptying, regulates postprandial glucagon, and reduces food intake.

Dosage. Liraglutide is given as a once-

daily injection in the abdomen, thigh, or arm. The initial dosage is 0.6 mg daily for the first week and can be titrated up by 0.6 mg weekly to a target dose of 3 mg daily. If a patient does not lose 4% of baseline body weight after 16 weeks on the target dose, the drug should be discontinued because it is unlikely to lead to clinically significant weight loss.

Efficacy. Liraglutide for weight management (3 mg once daily) was evaluated in a large (N = 3,731), randomized, double-blind, placebo-controlled international trial.[45] Participants did not have diabetes mellitus, but 60% had prediabetes. Liraglutide or placebo was given for 56 weeks, along with lifestyle counseling. At the end of the study, the liraglutide group had lost a mean of 8.4 kg vs 2.8 kg in the placebo group. Additionally, 63% of the liraglutide group lost at least 5% of body weight vs 27% in the placebo group, and 33% lost at least 10% of body weight vs 10% in the placebo group.

A 2-year extension found systolic blood pressure decreased with no change in pulse, and the prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%, respectively.[46] At 2 years, mean scores for physical function, self-esteem, and work had improved more in the liraglutide group than the placebo group.[47]

Adverse effects. The most common adverse reactions with liraglutide were nausea, vomiting, diarrhea, constipation, hypoglycemia, and loss of appetite. In most cases, nausea and vomiting were tolerable, transient, and associated with greater weight loss but not with decreased quality-of-life scores. Serious adverse reactions included pancreatitis, gallbladder disease, renal impairment, and suicidal thoughts.

CHOOSING A DRUG

For obese patients, when lifestyle modifications do not result in the desired weight loss, pharmacotherapy is an option. Practitioners have several FDA-approved options for weight management. Because of evidence that these drugs can postpone the onset of other complications and improve metabolic and cardiovascular parameters, they should be considered.

In phase 3 trials, these drugs caused modest weight loss of 5% to 10% of body weight. More weight was lost with the combination of phentermine-topiramate than with the other drugs.

In a 2016 meta-analysis, these drugs were associated with at least 5% weight reduction compared with placebo.[48] Phentermine-topiramate and liraglutide were most likely to produce at least a 5% weight loss, while liraglutide and naltrexone-bupropion were most likely to be discontinued because of adverse events. Combination drugs may have the advantages of synergistic effects on weight loss and fewer adverse reactions because lower doses of the individual drug components are used.

Response to therapy with most of these drugs should be evaluated at 12 weeks on the maintenance dose. If less than 5% weight loss has been achieved, the medication should be discontinued.

Adverse-effect profiles, drug interactions, abuse, misuse, and overdose potential should be considered when prescribing these drugs. Weight-loss drugs are contraindicated in pregnancy because they offer no potential benefit to a pregnant woman and may harm the fetus.

A negative pregnancy test is needed before women of childbearing age take topiramate, and monthly thereafter

The development of new drugs and better drug combinations is expected to provide more effective therapeutic strategies, which are essential for combating the obesity epidemic.

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