

Weight-Loss Pharmacotherapy: A Brief Review

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The prevalence of obesity has significantly increased during the past 30 years. In 2004, > 30% of U.S. adults were classified as obese.¹ Obesity is associated with many other chronic illnesses, including diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea.² Modest weight loss of 5–10% has been shown to improve insulin sensitivity, improve glycemic control, and delay the onset of diabetes.³ However, weight loss is difficult for many patients to achieve. This article reviews current pharmacological options for weight loss and provides a brief synopsis of potential future options.

Weight regulation is a complex system of multiple overlying feedback systems. In the simplest terms, obesity results from greater energy intake than energy expenditure, although this balance is affected by genetics and environmental and cultural factors. Three primary mechanisms may be altered to reverse the state of greater energy intake than energy expenditure: food intake, nutrient handling, and energy expenditure (Figure 1). Many of the available and pending weight-loss medications address one of these three mechanisms; they either reduce appetite, decrease nutrient absorption, or increase thermogenesis.

Weight-loss medications are recommended, unless contraindicated, for patients who have a BMI ≥ 30 kg/m² or > 27 kg/m² with obesity-related comorbidities.⁴ Medications should be combined with nutrition education, behavioral intervention, an exercise program, and a long-term weight-maintenance plan. The addition of these

lifestyle modifications to weight-loss pharmacology results in greater weight loss and treatment satisfaction.⁵ In general, weight-loss medications have a modest effect; this may be because of the complex regulatory system designed to prevent starvation.⁶

Weight-Loss Medications

Weight-loss medications have had a tainted past. Among the first medications to be used for weight loss were thyroid hormone (1893) and digoxin (1940s), with disastrous results.⁷ The most infamous weight-loss medication is fenfluramine (part of the phentermine-fenfluramine combination known as “phen-fen”), which was pulled from the U.S. market in 1997 because of its association with valvular heart disease.⁸

However, many other weight-loss medications have also been pulled from the market. The first was dinitrophenol in 1934, because of an association with the development of cataracts and neuropathy.⁹ In addition to prescription medications, the U.S. Food and Drug Administration (FDA) has also removed common over-the-counter weight-loss medications from the market, including ephedra (ma-huang) because of its cardiovascular effects, and phenylpropylamine, because it increased the risk of hemorrhagic stroke.^{10,11}

There are other negative associations with weight-loss medications. In 1937, amphetamines were used to treat obesity and were associated with abuse.¹² Since that time, medications with chemical structures similar to amphetamines have been avoided, regardless of whether abuse potential exists.

In addition to the often-negative view of weight-loss medications are their relative lack of efficacy. Most weight-loss medications result in a 5–10% weight loss.¹³ Many of these are approved for short-term use only, and when stopped, the weight is regained. However, many patients have obesity and obesity-related comorbidities that would be improved with modest weight loss. For some of these patients, the benefits of pharmacotherapy for weight loss may outweigh the risks.

Appetite-Altering Drugs

Several categories of medications alter appetite, including the sympathomimetics, serotonergics, endocannabinoid antagonists, and others. When discussing

IN BRIEF

The medical treatment of obesity is aimed at decreasing appetite, altering absorption of calories, and increasing thermogenesis. Two agents are available for the long-term treatment of obesity: sibutramine, a centrally acting anorectic agent, and orlistat, which blocks the absorption of fat by inhibiting the enzyme lipase. Agents approved for short-term treatment include the central anorectic agents phentermine and diethylpropion. Other agents, including endocannabinoid system antagonists, anti-epileptic agents, and combination therapies, are under investigation.

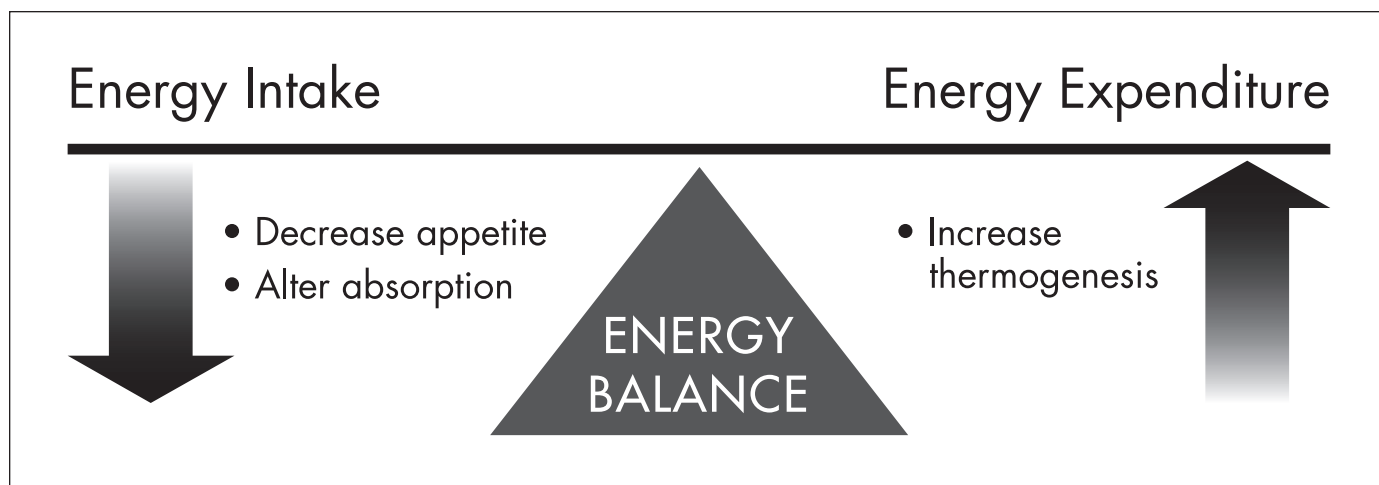


Figure 1. Pharmacotherapy targets in obesity

appetite, it is important to appreciate two distinct concepts of hunger. The first—satiety—refers to the sensation of feeling full when eating. A greater satiety means that a person hastens the cessation of eating. The second component of appetite is satiation, which is the length of time a person feels full after eating. Increased length of time between meals is referred to as increased satiation. If a drug reduces the time to satiety by half, but the patient eats twice as many meals, this will not lower total caloric intake. This concept is one of the reasons the phen-fen combination worked as well as it did. Phentermine is a sympathomimetic agent and increases the time between meals, whereas fenfluramine is a serotonergic agent that hastens the time to cessation of eating.¹⁴

All of the FDA-approved weight-loss medications that affect appetite are believed to act in the central nervous system to reduce caloric intake. However, there are other potential drug targets that may reduce appetite, including peripheral satiety and adipose signals.¹⁵

The centrally acting anorectics—sympathomimetic and serotonergic agents—were the first classes of medications to be approved for weight loss. As described above, both reduce caloric intake. All of the centrally acting

anorectic agents except mazindol are derivatives of β -phenylethylamine similar to dopamine, norepinephrine, and epinephrine.¹⁶ Amphetamines have a similar chemical structure. These agents also have a wide range of effects. Some agents, such as phentermine, diethylpropion, and phendimetrazine, are similar to amphetamines and stimulate the release of norepinephrine, whereas other agents, such as dexfenfluramine and fenfluramine, affect serotonin release and reuptake.^{16,17} Sibutramine is in the middle of the spectrum and blocks the reuptake of norepinephrine, serotonin, and dopamine.¹⁸

In addition to the sympathomimetic and serotonergic agents, some anti-epileptic agents and antagonists to the endogenous endocannabinoid system (ECS) also reduce appetite. Topiramate is the most studied anti-epileptic agent in weight loss, although its exact mechanism of action is unknown.¹³ Another anti-epileptic agent, zonisamide, has also been found to have significant weight-loss effects.¹⁹ Zonisamide is believed to have dopaminergic and serotonergic activity, although its exact mechanism also remains unclear. No antagonist to the ECS has been approved by the FDA, although rimonabant is approved in the European Union. There have been concerns about the safety of rimonabant,

namely increases in depressive and other psychiatric symptoms.²⁰

Specific agents that reduce appetite

Phentermine was approved by the FDA in 1959 for short-term use in the treatment of obesity. In a recent meta-analysis, the expected weight loss greater than placebo was 3.6 kg (95% confidence interval [CI]: 0.6–6.0 kg).¹³ Possible side effects of phentermine include tachycardia, palpitations, elevated blood pressure, and gastrointestinal side effects. Phentermine is contraindicated in patients with recent acute myocardial infarction and uncontrolled hypertension.

Diethylpropion is similar in structure to bupropion, a drug used to treat depression and tobacco abuse. Like phentermine, diethylpropion is approved by the FDA for short-term treatment of obesity. The above-mentioned meta-analysis found that diethylpropion users lost an average of 3.0 kg (CI –1.6 to 11.5 kg) greater than placebo.¹³ The side effects of diethylpropion are similar to those of amphetamines and include central nervous system stimulation, headache, insomnia, rash, and mild increases in heart rate and blood pressure.

Sibutramine is a newer agent and one of two drugs that is FDA-approved for long-term obesity treatment. The

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Table 1. Weight-Loss Medications

Drug	Common Dosage	Weight Loss Over Placebo (kg)	Side Effects	Contraindications	Monitoring
Phentermine	15–30 mg/day	3.6 (CI 0.6–6.0)	Tachycardia, palpitations, elevated blood pressure, insomnia, and gastrointestinal side effects	Recent acute myocardial infarction, uncontrolled hypertension, and hyperthyroidism	Blood pressure and heart rate
Diethylpropion	75 mg/day	3.0 (CI –1.6 to 11.5)	Central nervous system stimulation, headache, insomnia, rash, and mild increases in heart rate and blood pressure	Allergy to bupropion	Blood pressure and heart rate
Sibutramine	10–20 mg/day	4.5 (CI 3.6–5.3)	Headache, constipation, nausea, and insomnia. In some patients, substantial blood pressure elevation and increase in heart rate (4 beats/minute)	Uncontrolled hypertension, coronary artery disease, and other vascular disease	Blood pressure and heart rate
Topiramate	92–196 mg/day; may be divided into twice-daily doses	6.5 (CI 4.8–8.3)	Somnolence, memory effects, dizziness, paresthesias, changes in taste, nausea, metabolic acidosis, and secondary angle-closure glaucoma within 1 month of initiation		Serum bicarbonate and other electrolytes; symptoms of secondary glaucoma
Zonisamide	Start 100 mg/day; titrate to 400–600 mg/day	5.0 (CI 0.62–9.4)	Cognitive effects, somnolence, dizziness, and nephrolithiasis	Hypersensitivity to sulfonamides	Blood urea nitrogen and creatinine

longest randomized controlled trial of sibutramine lasted 54 weeks. The recent meta-analysis found that sibutramine users lost an average of 4.5 kg (CI 3.6–5.3 kg) compared to placebo at 54 weeks.¹³ The most common adverse effects of sibutramine are headaches, constipation, insomnia, and nausea. In some patients, there is a risk for a substantial increase in blood pressure and heart rate. Patients should be monitored closely for increases in blood pressure and heart rate after initiation of sibutramine. Sibutramine is contraindicated for patients with uncontrolled hypertension, coronary artery disease, or other vascular disease.

Topiramate is FDA-approved for the treatment of seizures. Its exact mechanism of action is unknown. Topiramate has been noted to have a side effect of weight loss. Nine studies have assessed topiramate’s weight-loss efficacy. The meta-analysis included six of these studies and found that patients on topiramate therapy lost an average 6.5 kg (CI 4.8–8.3 kg) more than those on

placebo. Higher dosages are associated with greater weight loss. In addition, there is some evidence that topiramate may be efficacious in the treatment of binge eating disorder.²¹ The most common side effects of topiramate are fatigue, memory effects (“word searching”), paresthesias, and changes in taste. In addition, patients using topiramate are at risk for secondary acute angle glaucoma during the first month of therapy. Topiramate is also associated with decreases in serum bicarbonate and development of metabolic acidosis. Electrolytes should be monitored during topiramate therapy. However, topiramate is not FDA-approved for the treatment of obesity or binge eating disorder.

Zonisamide is another FDA-approved agent for the treatment of seizures. Zonisamide has dopaminergic and serotonergic activity.²² There is one published randomized controlled trial of zonisamide in weight loss.¹⁹ In that study, zonisamide use was associated with an average 5.0 kg (CI 0.62–9.4 kg) greater weight loss than placebo. The

most common side effects of zonisamide are cognitive effects. There is also limited evidence that zonisamide may be efficacious in the treatment of binge eating disorder.²³ Again, zonisamide is not FDA-approved for the treatment of obesity or binge eating disorder.

Absorption-Altering Drugs

A parallel to decreasing caloric intake is to reduce the absorption of nutrients in the gastrointestinal system. The two most common drugs that alter absorption are orlistat and acarbose. Orlistat is a lipase inhibitor that reversibly inhibits human gastrointestinal lipases and is FDA-approved for the long-term treatment of obesity. Orlistat effectively blocks 30% of fat absorption.²⁴ It is not absorbed and therefore does not have any systemic effects, although the gastrointestinal side effects may be substantial.²⁵ Acarbose is FDA-approved for the treatment of type 2 diabetes and is an α -glucosidase inhibitor. Acarbose delays absorption of carbohydrate in the small intestine.²⁶ It lowers postprandial glycemia, but it has

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little weight-loss effect and therefore is not an obesity treatment.²⁷

Orlistat is the most studied weight-loss medication. In a recent meta-analysis that included 29 studies, orlistat was associated with an average increased weight loss of 2.9 kg (CI 2.3–3.5 kg) over placebo. The most common side effects are diarrhea, flatulence, bloating, abdominal pain, and dyspepsia. One study suggested that psyllium (6.0 g before bed) could reduce most of the unpleasant gastrointestinal side effects.²⁸

Thermogenesis-Increasing Drugs

No agent that specifically increases thermogenesis (basal metabolic rate) is available. However, several agents display thermogenic properties. The mechanism of weight loss with sibutramine is often proposed to be by both decreasing appetite and increasing energy expenditure through thermogenesis.²⁹ A recent study found that the use of sibutramine increased thermogenesis after 12 weeks, whereas patients in the placebo arm had a decrease in thermogenesis.³⁰ In addition, sibutramine has been shown to limit the decrease in resting energy expenditure often associated with weight loss.^{31,32}

Some of the centrally acting anorectic agents also display thermogenic properties. Like sibutramine, mazindol is thermogenic in animal models.^{33–37} These two agents appear to have most thermogenetic properties of the centrally acting anorectics, but diethylpropion and fenfluramine also have thermogenic properties in animals.^{33,35} Thermogenesis is said to be present because there is stimulation of oxygen consumption or norepinephrine turnover. Unfortunately, the studies in humans are often contradictory, and therefore it is difficult to confirm the animal models of thermogenesis in humans.^{32,38–42}

One of the most studied thermogenic agents is ephedrine (ephedra, or ma huang), which is no longer available on the U.S. over-the-counter market. Ephedrine causes weight loss by

reducing appetite and increasing thermogenesis.⁴³ Its mechanism of action is through both release of norepinephrine from the sympathetic nerve endings and as a direct agonist of β -receptors.⁴⁴ The β -receptors are involved in the peripheral thermogenic effect.⁴⁵ The thermogenic effects of ephedrine are synergistic with caffeine and aspirin.^{43,46} The use of these three medications became known as an “ECA stack.”

Agents on the Horizon

Several new agents are under investigation for weight loss. Some are drugs that are already FDA-approved for other indications; the manufacturers of many of these are seeking additional FDA-approved indications for weight loss. The U.S. Clinical Trials registration site (<http://clinicaltrials.gov/ct/gui/action/GetStudy>), when accessed on 12 July 2007, listed 291 studies in a search for “obesity treatment.” These studies include diet, exercise, behavioral, and pharmacotherapy treatments. Our knowledge of obesity treatment will continue to grow as more studies are completed.

Incretin mimetics have been used in the treatment of diabetes and have weight-negative effects. They are now being investigated as weight-loss medications. Pramlintide is an amylin analog currently used in the treatment of diabetes in conjunction with insulin therapy. Amylin is secreted by pancreatic β -cells with insulin. It slows gastric emptying, promotes satiety, and inhibits glucagon.⁴⁷ Pramlintide is now being investigated as a weight-loss agent in patients with non-insulin-requiring type 2 diabetes and obese patients without diabetes. In a recent Phase II study of obese patients with non-insulin-requiring type 2 diabetes, pramlintide use was associated with an average weight loss of 3.6 (\pm 0.6) kg greater than placebo.⁴⁸ Initial studies performed in obese patients without type 2 diabetes have shown that 45% of patients treated with 360 μ g of pramlintide twice a

day maintained a 10% weight loss from initial body weight at 12 months compared to 13% of the placebo group.⁴⁹

Another incretin mimetic, exenatide, is an analog of glucagon-like peptide 1 (GLP-1). GLP-1 is secreted by intestinal L-cells and is a potent stimulus of insulin secretion. In a meta-analysis, GLP-1 was found to acutely reduce food intake by 35%.⁵⁰ However, GLP-1 has a very short half-life. Exenatide, derived from the saliva of Gila monsters, has a much longer half-life and is approved for the treatment of type 2 diabetes.⁵¹ After 24 months, exenatide was associated with a weight loss of 4.7 kg (standard error 0.3 kg) in an uncontrolled study of patients with type 2 diabetes.⁵² To date, no studies of exenatide as a weight-loss agent in obese patients without diabetes have been published.

Lorcaserin is a serotonergic (5HT2c agonist) drug in phase III trials as a weight-loss agent. Phase I and II trials were promising and did not reveal cardiac valvulopathy.^{15,53,54} Lorcaserin has high affinity for the 5HT2c receptor, which is active in appetite control, and low affinity for the 5HT2b receptor, the activation of which is believed to be associated with cardiac valvulopathy.⁵⁵ Further studies are needed to determine this drug’s safety and efficacy.

Several combination drugs are also currently under investigation. According to pharmaceutical company press releases, a combination of bupropion SR and naltrexone SR, known as Contrave, is in phase III trials.⁵⁶ A combination of bupropion and zonisamide, known as Empatic, is in phase II trials.⁵⁷ A combination of phentermine and topiramate, known as Qnexa, is also in phase II trials.⁵⁸ There has also been interest in the combination of agents such as pramlintide, peptide YY3-36, and leptin.⁵⁹ Some believe that combination therapy is the most promising approach to overcome the body’s multiple overlapping systems to prevent weight loss.⁶⁰

Summary

Obesity is a common disease with a substantial burden on both individuals and the U.S. health care system as a whole.⁶¹ The medical treatment of obesity has been confounded by worrisome adverse events and modest efficacy. However, many overweight and obese patients benefit from modest weight loss. Current guidelines recommend considering weight-loss pharmacotherapy for patients with a BMI \geq 30 kg/m² or $>$ 27 kg/m² with obesity-related comorbidities.

New understanding of weight regulation and the complex interplay of the multiple overlapping systems—including the neuroendocrine axis, gut satiety signals, peripheral adiposity indicators, and the genetic, environmental, and cultural factors that influence obesity—have provided additional insight into potential therapeutic targets. Evidence suggests that targeting one pathway alone is unlikely to result in sustained weight loss and that combination therapies are needed. Combination therapies may include the combination of medications or the combination of one medication with intensive lifestyle modification therapy.

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