

Pharmacological Therapies for Obesity

Lee M. Kaplan, MD, PhD

*Massachusetts General Hospital Weight Center,
Department of Medicine and Gastrointestinal Unit,
Massachusetts General Hospital and Harvard Medical School,
50 Staniford Street, Boston, MA 02114, USA*

The development of effective pharmacological therapies has been both the greatest hope and one of the greatest disappointments in the field of obesity. At its root, obesity is a complex, but ultimately understandable, metabolic and behavioral disorder that disrupts normal body weight regulatory mechanisms. Logically, both the metabolic and behavioral components should be amenable to pharmacological treatment, and several agents have been developed that influence eating behavior, food intake, nutrient absorption, and energy expenditure. They also cause weight loss, but to a lesser extent and for a shorter period than would be considered ideal by either patients or physicians. Moreover, many of these agents have been associated with unacceptable adverse effects, in many cases as a direct result of their therapeutic mechanism of action. These adverse effects, including the euphoric and addictive effects of amphetamines, the hypertensive and arrhythmogenic effects of the adrenergic agents, the cardiac valvular effects of fenfluramine, and the steatorrhea associated with orlistat, have curtailed the use of these drugs significantly and in some cases have required their complete withdrawal from the market.

Recent studies of the physiology of body weight regulation have demonstrated the complexity of this control system and have identified numerous novel targets for therapeutic intervention [1,2]. These studies provide hope that new, more specific agents will provide more effective and durable treatment of obesity with fewer adverse effects. The very complexity of weight regulation; however, and the powerful systems to defend against real or perceived starvation, make it unlikely that a single pathway, cell or molecule will prove to be the Achilles heel of obesity. Thus, long-term

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E-mail address: lmkaplan@partners.org

effective treatment is likely to require a multi-modal approach, using multiple drugs aimed at different targets or novel combinations of specific pharmacological, nutritional, endoscopic, and surgical approaches.

Goals of pharmacological therapy

Available pharmacological treatments for obesity can be effective adjuncts to diet- and exercise-based behavioral therapies, typically increasing the amount of weight loss by 4% to 6% (eg, from a weight loss of 4% to a weight loss of 8%) over 1 to 2 years [3]. In all cases, however, the maximal effect appears to occur within the first year of therapy, often the first 6 months, with partial regain of lost weight thereafter [3,4]. In addition, the response to each medication varies widely from patient to patient, with a few patients (typically 2% to 5%) exhibiting considerably more weight loss than average and a significant portion experiencing no effect of the drug on their weight [5].

For the available weight loss medications (regardless of the mechanism of action), the criterion of a 4-pound weight loss in 4 weeks is a helpful guideline. Weight loss of lesser magnitude provides good evidence that the medication is having little effect. Given the potential for adverse effects, it is a strong indication for stopping the drug. For patients who lose 4 or more pounds in the first month, it is not clear how much additional weight loss should occur for the drug to be continued. Many physicians require that patients lose 4 pounds per month for a minimum of 3 months (12 pounds total) to consider the medication clinically effective. Thereafter, if a patient maintains the lower weight, the drug is still considered effective, because it is likely preventing the weight regain that occurs in more than 90% of patients upon cessation of treatment. For each of these drugs, human and animal studies suggest that they work less by causing weight loss than by causing the weight regulatory system to adjust the weight and energy set point downward. For each drug and for each patient, there appears to be a maximum achievable weight loss. Continuing the drug is usually necessary to maintain all or most of the lost weight, and cessation is commonly associated with rapid regain of the lost weight.

Weight loss medications usually are reserved for patients who have failed more standard behavioral interventions, including various combinations of diet- and exercise-based approaches. **Box 1** shows the standard criteria for use of these agents.

Medications approved for treating obesity

Table 1 lists the medications most commonly used for the treatment of obesity. The first three drugs, phentermine, sibutramine, and orlistat, are approved by the Food and Drug Administration (FDA) specifically for this

Box 1. Clinical criteria for pharmacological therapy for obesity

Body mass index (BMI) > 30 kg/m² or BMI > 27 kg/m² in association with significant medical complications
 Failure of behavioral approaches, including diet and exercise regimens
 No strong contraindications to the medication used
 For continued treatment, weight loss of ≥ 4 pounds per 4 weeks for each of the first 3 months

indication. The others are approved for other indications but have been found in one or more clinical studies to exhibit a significant weight loss effect. Two drugs, phendimetrazine and benzphetamine, are approved by the FDA but classified as Schedule III drugs by the Drug Enforcement Administration because of their high potential for abuse. These drugs have little or no role in the routine management of obesity and are not considered further in this article.

Phentermine

Phentermine is an adrenergic reuptake inhibitor that augments adrenergic signaling in the brain and peripheral tissues. It is thought to promote

Table 1
Medications for treatment of obesity

A. Approved by the FDA specifically for weight loss indication*

Medication	Typical dosing	Classification	Common adverse effects
Phentermine ^a	15–37.5 mg/d	Adrenergic agent	Tachycardia, hypertension
Sibutramine ^{a,b}	10–15 mg/d	Serotonergic/adrenergic	Hypertension, tachycardia
Orlistat	120 mg three times daily	Lipase inhibitor	Malabsorption, steatorrhea

B. Approved by the FDA for other indications**

Medication	Typical dosing ^c	Primary indications	Common adverse effects
Bupropion ^a	150–300 mg/d	Depression	Anticholinergic; agitation
Metformin	500–1000 mg/d	Type 2 diabetes	Hepatic oxidative injury
Topiramate	50–100 mg/d	Seizure disorder	Cognitive impairment
Zonisamide	400–600 mg/d	Seizure disorder	Cognitive impairment

* Phentermine is approved by the FDA for short-term use, and sibutramine and orlistat are each approved without time limitation [6]. Use in clinical practice varies widely.

** These agents typically are approved for life-long use for their specific indication.

^a Use of phentermine, sibutramine or bupropion in patients taking monoamine oxidase inhibitors (MAOIs) is strongly contraindicated because of the risk of severe cardiovascular events.

^b Use of sibutramine in patients taking serotonin-selective reuptake inhibitors (SSRI) is relatively contraindicated because of the risk of serotonin syndrome.

^c Typical dosing for use as a weight loss agent. Effective doses for primary indication may be higher.

weight loss by activation of the central and sympathetic nervous systems, with a resulting decrease in food intake and increased resting energy expenditure.

Phentermine is the weak but safe half of the “phen-fen” combination therapy introduced by Weintraub et al in the 1990s. Unlike fenfluramine, phentermine has no known effects on cardiac valves. As an adrenergic agonist, however, it can be associated with tachycardia, and, less commonly, hypertension. Thus, phentermine should be used with caution in people at significant risk for hemodynamic or cardiovascular complications of tachycardia and those with uncontrolled hypertension. All patients taking this medication should be monitored closely for changes in heart rate or blood pressure, particularly during the first several weeks of therapy and at times of dosage elevations. Abnormal heart rate or blood pressure should be treated as necessary, or the phentermine should be withdrawn.

Because phentermine no longer is covered by patent protection and there are several proprietary and generic formulations available, it is the least expensive of the widely used medications for weight loss [7]. It comes in two major forms, phentermine resin (eg, Ionamin) and phentermine-HCl. Normal dosing is 15 to 30 mg per day for phentermine resin and 18.75 to 37.5 mg per day for phentermine-HCl. An acceptable therapeutic response is considered as 4 pounds/4 weeks for at least the first 8 to 12 weeks of therapy, when given with or without associated dietary and exercise counseling.

Although approved by the FDA for only 3 months' use, many experts advocate longer-term use in patients who demonstrate a good therapeutic response during the first 3 months. As with other weight loss medications, the weight loss generally stops within 3 to 6 months of initiation. For patients who have lost a significant amount of weight during this time, continuation of the drug is nonetheless valuable to prevent weight regain.

Sibutramine

Sibutramine, a monoamine reuptake inhibitor, enhances adrenergic, serotonergic, and dopaminergic signaling in the brain. Thus, it has pharmacological characteristics that are similar to, if weaker than, those of the phentermine–fenfluramine combination that was introduced in the mid-1990s. Unlike fenfluramine, which has been withdrawn because of the risk of carcinoid-like cardiac valvular disease, sibutramine's serotonergic effects have not been associated with valvular abnormalities [8].

Sibutramine treatment is associated with an average weight loss of approximately 5% to 8%, compared with 2% to 4% in participants receiving placebo [9]. Most of the randomized, controlled trials include dietary or exercise counseling for participants in the treatment and placebo groups, which likely accounts for the weight loss in the placebo group. Thus, sibutramine itself appears to be associated with an average weight loss of approximately 3% to 4% during the first 6 to 12 months of treatment.

Extension of therapy for up to 2 years is associated with an average regain of approximately half of the weight lost initially. In one large trial, however, of the participants who experienced at least 5% weight loss on sibutramine, more than 25% maintained the full weight loss when sibutramine treatment was continued for an additional year [10]. As with other pharmacological therapies for obesity, however, there is a wide patient-to-patient variation in response. A small percentage of patients exhibits dramatic weight loss, and a significant number accrue no weight loss benefit at all [5]. To date, no reliable predictors of outcome after sibutramine or other weight loss medications have been identified.

The normal dosing for sibutramine in adults is 10 to 15 mg per day taken once daily. Many physicians prefer to start with 10 mg per day and increase to 15 mg per day as clinically required. Doses higher than 15 mg per day have not been demonstrated to have increased efficacy, and they are associated with a greater risk of adverse effects, most notably hypertension and tachycardia. Patients who lose at least 4 pounds in 4 weeks are considered sibutramine responders; this medication generally is continued in these individuals for as long as weight loss continues at this rate. With longer-term sibutramine therapy, weight loss generally stops after approximately 3 to 6 months. Nonetheless, for patients who have lost a significant amount of weight by this time, continuing treatment appears to decrease the rate and magnitude of weight regain. During the second year of continued therapy with sibutramine, patients typically regain approximately 50% of the initial weight lost [10]. As with initial weight loss, however, there is substantial patient-to-patient variation. Many obesity specialists will continue to use this medication in individual patients for as long as weight loss persists, extending on occasion beyond 2 years of treatment. Some practitioners prefer to use this medication on an intermittent, as needed, basis, although the efficacy of this approach has not yet been examined carefully.

In most patients, the major adverse effects of sibutramine relate to its adrenergic properties. Approximately 10% to 15% of patients experience new-onset hypertension that can be managed by antihypertensive therapy; fewer than 3% of patients need to discontinue this drug because of uncontrolled hypertension [11]. Patients with pre-existing hypertension undergoing sibutramine therapy need to be monitored closely for exacerbation of their hypertension; their antihypertensive regimens should be adjusted as required. A few patients exhibit tachycardia with sibutramine, and this drug should be avoided in patients at elevated risk for life-threatening tachyarrhythmias and those who are unlikely to tolerate tachycardia of any cause. Other, generally less severe and dangerous adverse effects include insomnia and anticholinergic-like effects such as dry mouth and constipation.

Use of sibutramine in patients taking serotonin-selective reuptake inhibitors (SSRIs) is relatively contraindicated because of an increased

risk of serotonin syndrome, which is marked by some combination of flushing, diarrhea, and mild hypotension [12]. As a result, sibutramine should only be prescribed to patients on SSRIs when both agents are indicated strongly and when the patient is supervised closely by a physician well-versed in the use of these agents taken alone and in combination.

Orlistat

Orlistat, an inhibitor of pancreatic and intestinal lipases present in the intestinal lumen, prevents the breakdown of ingested triglycerides into absorbable fatty acids and monoacylglycerols. When taken with meals, orlistat is capable of inhibiting the absorption of up to 30% of ingested fat [13]. Clinical trials have revealed that orlistat treatment (120 mg three times daily with meals) in the setting of nutritional counseling is associated with a weight loss of approximately 10% at 1 year [14,15]. Subjects receiving a placebo along with the counseling lost nearly 6%, suggesting that orlistat itself is responsible for approximately 4% body weight loss on average [14–17]. Extension of orlistat therapy to 2 years is associated with a regain of approximately one-third of the weight initially lost, versus regain of two-thirds of the initial loss in those who took placebo during the second year [14,15]. Some clinicians preferentially prescribe orlistat to patients who consume a high-fat diet; there is no evidence, however, that such patients respond better to this agent. Moreover, although conceptually attractive, there is no good evidence that the diminishing effects of orlistat in the second year of treatment results from substitution of carbohydrates for fats in the patients' diets. Some patients decrease their intake of fats to limit the gastrointestinal (GI) adverse effects of the drug, but there is substantial intake fat (and fat malabsorption with orlistat) even on such low-fat diets.

As seen with other approaches and medications, weight loss from orlistat treatment is associated with improvements in several comorbidities of obesity, including high blood pressure, insulin resistance, and serum lipid levels [3,17]. The magnitude of weight loss on orlistat is somewhat less in patients with type 2 diabetes mellitus, a phenomenon seen with several therapies for obesity [18]. Widespread use of orlistat is inhibited by its limited efficacy and the high rate of GI adverse effects. These side effects include flatulence, steatorrhea, increased stool frequency, fecal incontinence, and oily rectal discharge. The associated malabsorption can lead to deficiencies of the fat-soluble vitamins A, D, E, and K, and all patients on orlistat should receive a daily supplement enriched for these vitamins, given at least 2 hours before or after each orlistat dose. Because of the higher rate of vitamin D deficiency in people with obesity and the associated risk of metabolic bone disease, vitamin D levels should be measured before starting orlistat and periodically (eg, every 6 months) during therapy, with supplementation to achieve a serum 1,25-OH-vitamin D level of at least 20 IU/mL [1,3,16,17].

Medications approved for other indications

Bupropion

Unlike many other psychotropic agents that induce weight gain, bupropion treatment for depression often is associated with modest weight loss. In short-term trials (up to 26 weeks) in patients with obesity, bupropion SR has led to weight loss of 4% to 5%, compared with less than 2% in placebo-treated controls [19]. As with other weight loss-promoting drugs, short-term success may not translate into long-term weight loss, and longer studies are needed to assess the potential utility of bupropion for obesity. Nonetheless, given the paucity of pharmacological options, many providers are trying a course of bupropion, particularly for patients with mild-to-moderate obesity who have symptoms of depression. A growing use of this agent is as a replacement for one of the SSRIs, when those agents have led to significant weight gain. The mechanisms of action of SSRIs and bupropion for depression are different, however, and not all patients respond similarly to the two classes of drugs. For patients with SSRI-induced weight gain (which occurs more commonly with citalopram, escitalopram, and paroxetine), it is often effective to switch to another SSRI that is less likely to generate weight gain, such as fluoxetine or sertraline. It is important to note, however, that in different patients each of these agents can be associated with weight gain, weight loss, or have no effect on weight, so empiric evaluation of their effect is needed in each individual treated.

Metformin

Nearly all of the available medications to treat type 2 diabetes mellitus are associated with weight gain. Insulin therapy promotes an increase in fat deposition and total body fat, and sulfonylureas exert the same effect by enhancing secretion of endogenous insulin from pancreatic beta cells. Although the degree of weight gain varies, the amount can be substantial in some patients. The thiazolidinediones, including pioglitazone and rosiglitazone, typically cause only minor weight gain, but recent studies have suggested that body fat may be redistributed more centrally with their use. In contrast to these other agents, metformin (Glucophage and others) is either weight neutral or causes moderate weight loss. In the long-term Diabetes Prevention Program trial, the metformin-treated group lost approximately 4% of their initial body weight over 1 to 2 years, which was approximately half of the weight loss seen in the group that underwent an intensive lifestyle intervention. Although the effectiveness of metformin was diminished by year 4, weight loss remained significantly greater than the placebo-treated group. In this trial, metformin treatment led to a 31% decrease in the incidence of diabetes, compared with a 58% decrease for the lifestyle intervention group. Based on these results and similar outcomes in shorter duration studies, many clinicians recommend metformin as the agent of first choice in patients with

obesity and type 2 diabetes. In addition, metformin is being used with increasing frequency in nondiabetic patients with obesity and insulin resistance. One group worth specific mention is patients with obesity and non-alcoholic fatty liver disease. Animal studies and small series in people suggest that metformin treatment may decrease fat deposition in the liver. Whether these findings will be borne out in larger, controlled studies remains to be seen. Nonetheless, metformin-induced weight loss is likely to have a beneficial effect in these individuals. The normal dose of metformin is 500 to 850 mg, once or twice daily. Metformin should not be used in patients with significant renal dysfunction (creatinine of at least 1.5 mg/dL) or ketoacidosis; lactic acidosis is a rare but serious complication of metformin use.

Topiramate

Promotion of weight gain is the most troubling adverse effect of many of the newer antipsychotic drugs, mood stabilizers and anticonvulsants, and physicians using these medications have sought effective ways of mitigating this complication. Topiramate, an anticonvulsant with mood stabilizing properties, is unusual among these drugs in that it promotes weight loss rather than weight gain. In several uncontrolled studies, topiramate treatment has led to partial or complete reversal of weight gain induced by other psychotropic drugs. This effect recently led to the investigation of topiramate as a primary treatment for obesity. Although studies of this broader use are continuing, doses above 100 mg per day are associated with a high rate of cognitive impairment that is unacceptable to most patients. For reasons that are not clear, this effect appears less common or troubling in patients receiving other psychotropic agents. To avoid adverse effects, this medication should be started at low doses (eg, 25 mg per day) and increased slowly to a maximum of 100 mg per day. Although doses up to 200 mg per day commonly are used to treat seizures and mood disorders, the available data suggest that doses above 100 mg per day confer little additional weight loss and are associated with increased cognitive deficits.

Zonisamide

Zonisamide is an atypical anticonvulsant that has been found to induce weight loss in patients receiving other antiepileptic agents. This observation provoked a short-term, randomized, controlled trial that demonstrated significant weight loss in patients with moderate obesity (average BMI = 36 kg/m²). In this trial, patients receiving 400 to 600 mg per day zonisamide lost an average of 6% of their initial body weight, compared with a 1% loss in the control group [20]. The major adverse event reported in this study was fatigue. This study has generated much interest in zonisamide as a possible primary treatment of obesity. Confirmatory and longer-term studies are needed, however, before it can be recommended for widespread use.

Discredited medications

Fenfluramine

Fenfluramine and its biologically active enantiomer dexfenfluramine are monoamine secretagogues. They act by making more serotonin available at serotonergic synapses, and one effect of this increased synaptic serotonin is to diminish appetite and promote energy expenditure. The combination of fenfluramine and phentermine, an adrenergic agonist, was shown in the early 1990s to have dramatically improved effects (both numbers of positive responders and degree of weight loss) over either phentermine or fenfluramine alone [21,22]. Widespread use of this combination began in 1995 and was accelerated by FDA approval of dexfenfluramine for weight loss in 1996. In 1997, however, a high rate of cardiac valvular abnormalities, most notably fibrosis reminiscent of carcinoid/serotonin-associated heart disease, was seen in patients taking these agents [23,24]. Further epidemiological examination linked these abnormalities with the fenfluramine, which was withdrawn from the market. Phentermine, as noted above, remains in widespread use for obesity treatment. It has none of the valvular effects associated with fenfluramine. Notably, in the years since fenfluramine was withdrawn, the risk of associated valvular disorders has been re-evaluated and, while still significant, the risk has been found to be substantially lower than originally thought [25]. Fortunately, many patients who exhibited valvular abnormalities from this medication have experienced partial or complete regression of these changes since the drug was discontinued [24,25].

Ephedrine and phenylpropanolamine

These agents had been sold as over-the-counter weight loss remedies until they were withdrawn in 2000 and 2004, respectively, after the FDA determined that they were unsafe for routine use. Despite their widespread use in dietary supplements and herbal formulations, there have been few studies of their short- or long-term effectiveness in promoting weight loss. These agents have been associated with an increased risk of cardiovascular complications, including strokes and life-threatening arrhythmias, however, which led to the FDA recommendations that they be withdrawn [26–28]. Current formulations of dietary supplements and other OTC weight loss therapies sold in the United States do not include these compounds.

Pharmacological treatment of drug-induced weight gain

Many medications are associated with weight gain, including steroid hormones, thiazolidinediones, insulinotropic agents, and several classes of psychotropic drugs (Box 2). Treatment for drug-induced obesity is similar to

Box 2. Medications associated with weight gain*Steroid hormones*

Glucocorticoids

Progesterone

Neurotropic and psychotropic medications

Olanzapine, clozapine

Valproic acid

Lithium

Phenothiazines

Antidepressants

- SSRIs
- Tricyclics
- MAOIs

Diabetes treatments

Sulfonylureas

Insulin

Thiazolidinediones (Actos, Avandia)

that for essential obesity, with a heavy reliance on behavioral therapies to improve diet and increase physical activity. In some cases, however, drug-induced obesity may be more amenable to pharmacotherapy than other weight disorders. Weight gain associated with treatment of diabetes may be ameliorated or reversed by inclusion of metformin in the antidiabetic regimen, either in lieu of or in addition to thiazolidinediones or sulfonylureas. Although insulin, sulfonylureas, and thiazolidinediones promote weight gain and central fat redistribution, metformin often promotes weight loss. Even in the absence of weight loss, per se metformin tends to be weight-neutral, and substitution of other antidiabetic agents with metformin often results in modest weight loss. For patients with seizure or mood disorders in whom pharmacological treatment has been associated with significant weight gain, topiramate and zonisamide may be particularly helpful. Both of these agents are approved by the FDA for treatment of seizure disorders. In addition, they have been found to have mood stabilizing properties, making them reasonable alternatives to weight-promoting mood stabilizers such as olanzapine and clozapine. In some cases of seizure and mood disorders, it is possible to change from these latter medications to ones that have fewer weight-promoting effects, including topiramate and zonisamide. Alternatively, these weight loss-promoting mood stabilizers and anticonvulsants are often effective when added to the patient's regimen. Different practitioners follow widely different practice patterns relating to these medications. Where equivalent efficacy can be achieved with agents that inhibit further weight

gain (or promote reversal of previous obesity), this approach is generally favored.

Medication use after weight loss surgery

Although GI weight loss surgery is a highly effective therapy for severe obesity, its efficacy varies considerably among individual patients. After Roux-en-Y gastric bypass, patients lose an average of 65% to 70% of their excess body weight within the first 1 to 2 years after surgery and maintain the loss of 50% to 55% of their excess body weight over more than 10 years [29,30]. The author has observed, however, that weight loss in individual patients varies from 20% to 120% of excess body weight at 1 year. For many patients at the lower end of the weight loss distribution, the results of surgery are disappointing. Some clinicians have used medications in an attempt to enhance weight loss after surgery. No formal trials of this approach have been reported, but the centrally acting agents, including phentermine, sibutramine, and topiramate are attractive because of their ability to curb appetite in many patients. Orlistat in this setting appears inadvisable, because it can exacerbate deficiencies of fat-soluble vitamins already depleted by the surgery itself. Prescribing any weight loss medication after surgery should be viewed as experimental, however, and generally should be limited to controlled trials by clinicians experienced in obesity treatment.

Future considerations

The increasing understanding of the normal mechanisms of weight regulation has given rise to numerous targets for new pharmacological therapies, and more than 150 drugs are under active development for the treatment of obesity [31]. These newer agents act on a broad spectrum of available targets (Fig. 1), and most are more narrowly directed than currently available options; thus, there is hope that they will have a better adverse effect profile. Two of them, ciliary neurotrophic factor (CNTF) and rimonabant, were recently studied in large-scale, randomized controlled trials. CNTF is a central- and peripherally acting nerve growth factor that has been found to exhibit appetite suppressing activity in animal studies. In animal and human studies directly specifically at obesity, it has the distinction of being the first weight loss agent to exert effects that continue for some time after the drug is discontinued. Unfortunately, however, its use is associated with the development of neutralizing antibodies that limit its effectiveness and may be associated with immune complex disease.

Rimonabant is an antagonist of the cannabinoid type 1 receptor, one of two receptors that mediate the effects of endogenous cannabinoids and marijuana. It has been developed as an aid for smoking cessation and as

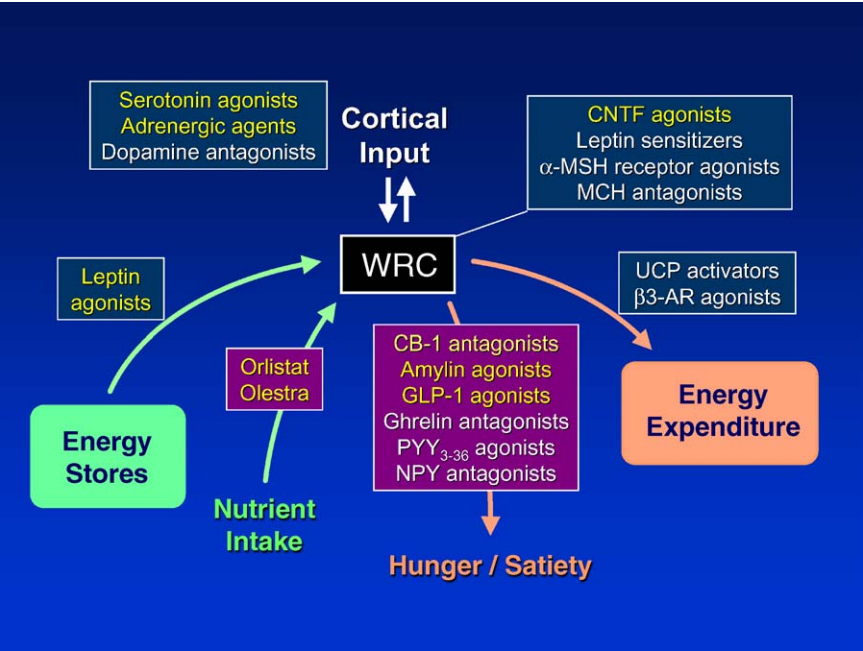


Fig. 1. Selected targets for obesity pharmacotherapy. Increased understanding of the mechanisms of normal weight regulation has revealed numerous potential targets for novel weight loss medications. Compounds that affect each of these targets are in varying stages of development. *Abbreviations:* β3-AR, beta-3 adrenergic receptors; CB-1, cannabinoid type 1 receptors; CCK-A, cholecystokinin type A receptors; CNTF, ciliary neurotrophic factor; GLP-1, glucagon-like peptide 1; MCH, melanin-concentrating hormone; α-MSH, alpha-melanocortin; NPY-Y1/Y5, neuropeptide Y type 1 or type 5 receptors; NPY-Y2, neuropeptide Y type 2 receptors; UCP, uncoupling protein; WRC, weight regulatory centers of the brain, including several nuclei within the hypothalamus, hindbrain, and reward centers.

a treatment for obesity. In one, as-yet-unpublished, large-scale clinical trial, treatment with 20 mg per day rimonabant for 1 year was associated with an increased rate of smoking cessation and an average weight loss of 18 pounds, compared with an 8-pound weight loss in the placebo group. It also was associated with a significant improvement in high-density lipoprotein cholesterol, suggesting that it may have broad benefits in reducing cardiovascular risk. Whether these effects are durable remains unknown, and additional long-term studies are needed to assess efficacy and safety. Nonetheless, this agent is an example of the potential for novel therapies aimed at specific targets within the body's weight regulatory apparatus.

Because the physiological mechanisms of weight regulation are complex, and redundant systems are likely to be present to guard against starvation, it is unlikely that any single agent will be completely effective in treating obesity. Effective long-term control of weight by pharmacological therapies

likely will require multiple agents used in combination to defeat the requisite number of redundant pathways. The large number of drugs under development suggests that several moderately effective agents will emerge. Combinations of different moderately effective agents, or combinations of these agents with other therapies (eg, dietary manipulation, intestinal infusions, electrical stimulation, or endoscopic or laparoscopic surgery), likely will generate the greatest sustainable weight loss. Design of some of these combinations will be guided by advancing knowledge about the physiological effects of weight loss surgery and the array of mechanisms used by this very effective treatment to induce durable weight loss. The identification of increasingly safe and effective medications for obesity likely will be the basis for new and even more effective combination approaches, even if they have limited utility as single agents. Such combinations should facilitate sufficient control of obesity in many patients to begin reversing this epidemic problem.

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