



# Management of Obesity: Role of Pharmacotherapy and Alternative Therapies

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## INTRODUCTION

Obesity is a chronic disease characterized by an accumulation of excess adipose tissue and associated with an increased risk of multiple morbidities and mortality. Weight loss prevents or tempers the severity of many obesity-related morbidities. When food intake is limited, counter-regulatory mechanisms cause an increase in appetite and a decrease in energy expenditure as protective measures against starvation, and make volitional weight loss by a hypocaloric diet difficult to achieve. Pharmacological intervention is, therefore, often necessary to aid in inducing weight loss and maintenance.

## CURRENTLY AVAILABLE PHARMACOTHERAPY

Pharmacotherapy should be considered in overweight and obese patients with a body mass index greater than 27 kg/m<sup>2</sup>, particularly in the presence of comorbidities such as type 2 diabetes or hypertension or an increased waist circumference when conservative measures such as behavior therapy, diet, and exercise have not resulted in the desired weight loss. A realistic treatment goal is usually loss of 5–10% of initial body weight over a 6- to 12-month period, followed by long-term maintenance of reduced weight. Most cardiovascular risk factors are improved even at this level of modest weight reduction because of the predominant loss of visceral fat leading to disproportionate improvement in the risk of developing complications. The NIH guidelines recommend that if a chosen medication does not lead to a 2-kg weight loss in the first month of treatment, the dose should be adjusted or the medication discontinued. Only two drugs, sibutramine and orlistat are approved by the US FDA for long-term use.

Sibutramine inhibits norepinephrine and serotonin reuptake. Sibutramine has been found to reduce body weight and appetite and increase satiety. More than 10 prospective, randomized, controlled trials of sibutramine have supported its efficacy. An analysis of three trials of at least 1-yr duration shows that patients on sibutramine lost 4.3 kg or 4.6% more weight than those taking placebo. The most common adverse effects are dry mouth, constipation, and insomnia. On the average, systolic blood pressure increases by 4 mm Hg, and diastolic blood pressure by 2–4 mm Hg. Heart rate increases about 4 beats/min. Despite these changes, the safety and efficacy of sibutramine have been demonstrated in subjects with controlled hypertension; however, it is recommended that blood pressure and pulse rate be monitored regularly. The use of sibutramine is contraindicated

in individuals with uncontrolled hypertension or cardiovascular disease or with concomitant use of monoamine oxidase inhibitors or other serotonin reuptake inhibitors. To date, there has been no association between the use of sibutramine and valvular heart disease, as became evident with the use of fenfluramine.

Orlistat, an inhibitor of pancreatic and gastrointestinal lipases, prevents the absorption of approximately 30% of dietary fat. Pooled results of 11 prospective randomized controlled trials demonstrate that subjects treated with orlistat displayed a 2.7-kg or 2.9% greater reduction in weight than placebo-treated patients after 1 yr of follow-up. Orlistat reduces low density lipoprotein and cholesterol levels independent of reductions in body weight, decreases the progression to a diabetic state, and leads to better glycemic control in patients with diabetes. Side effects due to the mode of action include oily spotting, liquid stools, fecal urgency or incontinence, flatulence, and abdominal cramping. As orlistat may impair the absorption of fat-soluble vitamins, a multivitamin supplement should be taken 2 h before or after the medication.

## OTHER DRUGS TESTED IN CLINICAL TRIALS

A number of other drugs have been tested in preclinical and clinical trials. Metformin, approved for the treatment of type 2 diabetes, was studied in the Diabetes Prevention Program Research Trial as a means to prevent the development of diabetes in nondiabetic persons with elevated fasting and post-load plasma glucose concentrations. Although less successful than a lifestyle modification program, treatment with metformin was associated with a 2.1-kg mean weight loss and a decrease in the incidence of diabetes by 31% compared with placebo treatment over the average follow-up period of 2.8 yr. Metformin may, therefore, be considered as adjunctive therapy in individuals at high risk for progression to diabetes.

Two antiepilepsy drugs, topiramate and zonisamide, and the antidepressant bupropion have also been studied for weight loss effects. In a randomized, double-blind, placebo-controlled trial, the mean percent weight loss was –2.6% in placebo-treated subjects *vs.* –6.3% in subjects treated with 192 mg/d topiramate for 24 wk. Topiramate has also been effective in the treatment of binge eating disorder. The frequency of adverse events, mostly related to the central and peripheral nervous system, such as paresthesias, somnolence, and difficulty with memory, has led to the termination of phase III trials while an extended release formulation is being developed by the manufacturer. As

the use of topiramate may also cause a nonanion gap metabolic acidosis, it is recommended that serum bicarbonate levels be checked before initiating therapy and periodically thereafter. The efficacy of zonisamide on binge eating is currently under study. The mechanisms by which these antiepileptic drugs produce weight loss are unclear, but may be due to antagonism of the glutamate kinate receptor by topiramate and to the serotonergic and dopaminergic activities of zonisamide.

The use of leptin to induce weight loss proved disappointing. Administration of leptin at a high dose resulted in weight loss of 5.8 kg after 24 wk, but was associated with an unacceptable incidence of injection site reactions. A longer-acting form of pegylated leptin produced additional weight loss compared with placebo in severely, but not moderately, energy-restricted subjects. Manipulation of the leptin signal transduction pathway may be an alternative approach to weight loss therapy. An intriguing possible use for leptin may be as an adjunctive therapy for the maintenance of weight loss. The reductions in energy expenditure and thyroid hormone concentrations that occur with weight loss may be due to a decline in leptin concentrations and may also hamper the ability to maintain weight loss.

Ciliary neurotrophic factor (CNTF) was originally developed as a potential treatment for amyotrophic lateral sclerosis, but was found to produce anorexia and weight loss. CNTF reduces food intake through down-regulation of appetite-stimulating neuropeptides within the hypothalamus in both leptin-responsive and leptin-resistant rodents. Prevention of binge-overeating and continued weight loss after the drug is stopped suggest that CNTF may reduce the hypothalamic body weight set-point in rodents, but raises some questions as to possible long-term central nervous system effects in humans.

Endocannabinoids stimulate food intake through CB1 cannabinoid receptors in the hypothalamus. An antagonist of the CB1 receptor, SR141716A or rimonabant, suppresses food intake in genetically obese and diet-induced obese animals. In a multicenter, double-blinded, phase III trial, 44% of subjects lost greater than 10% of body weight at 1 yr compared with 10% of subjects taking placebo.

## FUTURE POTENTIALS

Over 100 molecules are in various stages of preclinical and clinical development. The discovery of leptin and how it regulates other peptides involved in energy homeostasis has opened a new spectrum for drug development. Leptin is secreted by adipocytes and affects the synthetic pathway of both anorectic (appetite-suppressing) and orexigenic (appetite-stimulating) peptides. The expression of neuropeptide Y (NPY) and agouti-related protein, potent orexigenic peptides produced in the arcuate nucleus of the hypothalamus, is down-regulated by leptin.

Recognition of the importance of the hypothalamus in the regulation of energy homeostasis has led to the targeting of neuropeptides and their receptors in this region for weight loss therapies. NPY receptor antagonists are in early clinical trials for obesity treatment. Although acting at different receptors within the arcuate nucleus, the actions of leptin and insulin appear to overlap, possibly due to convergence upon a single intracellular signal transduction pathway known as the insulin receptor substrate phosphatidylinositol 3-kinase pathway. Central

administration of insulin or insulin mimetics reduces food intake and body weight, whereas impairment of hypothalamic insulin receptors causes hyperphagia and insulin resistance. Insulin and leptin have a cooperative anorectic effect.

Molecules within other regions of the hypothalamus influence energy balance. Melanin-concentrating hormone (MCH) is present in the lateral hypothalamus. Expression of MCH is increased with fasting and leptin deficiency. Disruption of the *MCH* gene or administration of an MCH1 receptor antagonist results in hypophagia and leanness in rodents. Such antagonists may be useful in the treatment of human obesity. Other molecules within the hypothalamus include corticotrophin and TSH releasing hormones, and orexin A and B. As many of these hormones have pleiotropic effects, manipulation of their activity to produce weight loss without causing undesirable behavioral and metabolic responses will prove to be a challenge.

Our increased understanding of the neurohormones secreted by the gastrointestinal tract has provided us with other possible drug therapies for obesity. Peptide YY<sub>3-36</sub> (PYY) is secreted postprandially in proportion to the calories ingested by endocrine L cells lining the distal small bowel and colon. Obese individuals exhibit a blunted postprandial PYY response compared with that in lean subjects. PYY decreases food intake through a gut-hypothalamic pathway that involves inhibition of NPY Y2 receptors in the arcuate nucleus and the dorsal motor nucleus of the vagus nerve. The release of PYY acts as an “ileal brake”, suppressing gastric motility that probably induces a sense of satiety to promote meal termination.

Premeal hunger and meal initiation are stimulated by interactions between gut hormones and the hypothalamus. Ghrelin is an acylated peptide secreted by oxyntic cells in the stomach fundus. Originally described as a GH secretagogue, the putative role of ghrelin in energy homeostasis has more recently been identified. Circulating ghrelin concentrations increase preprandially and decrease postprandially, and infusion of ghrelin in humans induces increased appetite and food intake. Diet-induced weight loss is associated with an increase in plasma ghrelin levels that may contribute to increased hunger and difficulty with the maintenance of weight loss.

Meal termination may also be regulated by the postprandial release of oxyntomodulin, a 37-amino acid peptide that arises from posttranslational processing of proglucagon in the same intestinal cells that secrete PYY and glucagon-like peptide-1 (GLP-1). A single infusion of oxyntomodulin suppresses appetite and reduces food intake in humans over a 12-h period and is associated with a reduction in fasting ghrelin concentrations. The effects of oxyntomodulin on food intake may be mediated by the receptor for GLP-1. GLP-1 has also been shown to reduce gastric motility and short-term *ad libitum* energy intake and to increase satiety both in lean and overweight subjects. Treatment with the longer-acting GLP-1 agonist, exendin-4, decreases food intake and fat deposition and increases glucose tolerance in Zucker fatty rats.

Cholecystokinin (CCK), a peptide hormone released by the duodenum and jejunum in response to the presence of intraluminal digestive products, stimulates pancreatic secretion, gallbladder contraction, and intestinal motility and inhibits

gastric emptying. There are two distinct CCK receptor subtypes: CCK-A, which is primarily expressed in alimentary tissues and specific brain sites, and CCK-B, which is found mainly within the brain. CCK acts as a satiety signal via CCK-A receptors on afferent vagal fibers to the brain causing termination of an individual meal. Somatostatin is another gut peptide that inhibits gastrointestinal motility and endocrine and exocrine secretions, and may promote satiety. Treatment with octreotide, a long-acting somatostatin receptor agonist, attenuated the weight gain associated with pediatric hypothalamic obesity.

Other therapeutic options for the treatment of obesity may involve drugs that affect substrate utilization and energy partitioning rather than appetite and food intake. The beneficial effects of GH therapy on fat distribution and lean muscle mass in patients with GH deficiency have not been reproducible in individuals with common obesity and, in fact, is usually associated with an increase in insulin resistance. Adiponectin (also known as Acrp30 or AdipoQ) is an adipocyte-derived hormone that increases fatty acid oxidation in muscle and decreases fat accumulation in mice without significantly affecting food intake. Circulating levels of adiponectin are decreased in both rodent and human models of obesity and insulin resistance.

### CONCLUDING REMARKS

In the absence of effective preventive measures to curb the obesity epidemic and the failure of conservative approaches, we must look to more effective and safe pharmacotherapy for obesity treatment. The rapidly growing science of energy homeostasis gives hope that we are in store for exciting advances in obesity management. Therapies specifically targeted to newly discovered homeostatic pathways, such as the gut-hypothalamic axis, anorexic and orexigenic hormone receptors within the hypothalamus, effectors of leptin and insulin signal transduction, and central and peripheral nutrient sensing pathways, are possible. Effective weight loss and long-term maintenance of weight loss will probably require multidrug therapy that targets these different regulatory elements. We can anticipate that in the future we will amass an armamentarium for the pharmacological treatment of obesity that is at least as effective as the one we now have for treating the complications of obesity.

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