
Pharmacotherapy of Obesity

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Introduction

Recent population studies have shown that the age-adjusted prevalence of obesity, defined as a body mass index (BMI) ≥ 30 , has increased from 22.9% (NHANES III 1988–1994) to 30.5% (1999–2000; $p < 0.001$).¹ Obesity is associated with an increased risk of developing diabetes, heart disease, hypertension, lung disease, steatohepatitis, and certain types of cancer. Poor diet and physical inactivity are the second leading preventable cause of death in the U.S. behind smoking, accounting for 400,000 deaths per year.² It is impossible to find an organ system in the body that is not deleteriously affected by the burden of obesity. It is for these reasons that the management of obesity has become a priority for physicians of all specialties.

The Pharmacotherapy Niche

Obesity is a chronic disease that has not responded well to behavioral and dietary management. Pharmacological treatments for obesity have been tried over the years. Older therapies were associated with side effects, abuse, and relapse despite ongoing treatment — characteristics that have led most practitioners to steer clear of prescribing them. Newer treatments have produced more promising results. These are not habituating, have been studied long term, and have demonstrated proven health benefits. Nevertheless, they are not yet accepted by practitioners because they produce a 5% placebo-subtracted weight loss — less than desired — and are not uniformly reimbursed by insurance companies.

The failure of our present medical treatments to produce desirable results may be the result of a medication not being primarily effective, or it may be that counter-regulating mechanisms prevent further weight loss and encourage regain. Evidence now supports the concept that body weight is a regulated variable of the body, like blood glucose or blood pressure, and that attempts at weight loss are mitigated by counter-regulatory systems activated in an attempt to prevent starvation. It is important for the clinician to understand that the medi-

cation continues to be effective when a plateau in weight is reached, that increasing to a supratherapeutic dose rarely produces more weight loss and can lead to greater side effects, and that discontinuation of the medication will certainly lead to weight regain. Combinations of medications may produce better weight maintenance, but do not produce substantially greater weight loss in most circumstances.



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Risk-Benefit Ratio of Pharmacotherapy

Many physicians and patients are resistant to treating obesity, holding the new anti-obesity pharmaceuticals to unrealistic standards of safety and efficacy. While safety is of utmost importance with any drug, it is important to note that many diseases are treated with medications that carry a risk of side effects, because it is believed that the benefit to the patient is greater than the risk. The same standards should apply to anti-obesity drugs.

The two agents approved for long-term use, sibutramine (a norepinephrine and serotonin reuptake inhibitor that enhances satiety) and orlistat (a lipase inhibitor that reduces fat absorption), have proven effective in large-scale multicenter trials and have side effect profiles that can be readily monitored by clinicians (Table 1). Evidence from these trials suggests that, in appropriate patients who lose weight on these medications, the associated medical benefit can be significant. The key, therefore, is to treat patients where the benefit from weight loss is greatest, namely, those patients who are at greatest medical risk. The Diabetes Prevention Program Research Group best illustrated this concept.³ In that study, subjects at risk for type 2 diabetes who were randomized to a lifestyle-modification program (with the goals of at least a 7% weight loss and at least 150 minutes

Table I. Weight Loss Drugs Approved for Long-Term Use

Drug	Dose	Action	Adverse effects
Sibutramine (Meridia®)	5, 10, 15 mg 10 mg po qd to start, may be increased to 15 mg or decreased to 5 mg	Norepinephrine, dopamine, and serotonin reuptake inhibitor	Constipation, dry mouth, insomnia, headache, increase in heart rate and blood pressure
Orlistat (Xenical®)	120 mg 120 mg po tid before meals	Inhibits pancreatic lipase, decreases fat absorption	Decrease in absorption of fat- soluble vitamins; soft stools and anal leakage

Source: Adapted from the Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (2000), National Institutes of Health and the North American Association for the Study of Obesity, Bethesda, MD.

of physical activity per week) had an incidence of type 2 diabetes 58% lower than that of control subjects with no intervention.

Candidates for Pharmacotherapy

At present, pharmacotherapy is appropriate in individuals who are at medical risk from their level of obesity; have not responded to more traditional conservative management (such as diet, exercise, and behavioral change); have no contraindications to the use of the pharmacological agent; and who understand the risks, likelihood of success, and the need for long-term treatment. Clinical guidelines for obesity treatment developed by the National Institutes of Health (NIH) support the use of currently available medications as an adjunct to lifestyle therapies for patients with a BMI ≥ 30 who have no obesity-related co-morbidities. Pharmacotherapy may also be considered for patients with a BMI ≥ 27 if co-morbid conditions are present. Additionally, women with a waist circumference >35 in. and men >40 in. are also candidates for pharmacotherapy if co-morbid conditions are present.

Sibutramine

Sibutramine enhances satiety by blocking the reuptake of norepinephrine and serotonin in the central nervous system. It may also increase metabolic rate by activating the β_3 -adrenergic receptor peripherally. Bray et al. conducted a placebo-controlled trial to evaluate different doses of sibutramine over a 24-week period.⁴ They found a statistically significant weight loss at all doses (1, 5, 10, 15, 20, and 30 mg) as compared to placebo. Wirth and Krause showed that intermittent sibutramine was as effective as continuous sibutramine over a 44-week period.⁵ Several studies have shown that sibutramine is an effective agent in terms of weight loss and weight maintenance.

McMahon et al.⁶ and Sramek et al.⁷ each demonstrated the safety of sibutramine in the treatment of obese patients with well-controlled hypertension. In another study, Zan-

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nad et al. demonstrated that 6 months of sibutramine had no significant impact on cardiac dimension, valve function, or electrocardiograms.⁸ Sibutramine can increase both pulse and blood pressure, and monitoring of these vital signs should be performed on a monthly basis initially and every 3 months once the patient's weight has stabilized. The most frequent side effects associated with sibutramine are dry mouth, anorexia, and insomnia. The recommended initial dose of sibutramine is 10 mg once daily. The dose can be increased to 15 mg daily after 4 weeks.

Orlistat

Orlistat promotes weight loss by inhibiting the absorption of fat from the gastrointestinal (GI) tract. On average, 120 mg of orlistat taken three times per day will decrease fat absorption by 30%.⁹ Orlistat has been found to be more effective in inhibiting the digestion of solid foods, as opposed to liquids.¹⁰

In the recent XENDOS trial,¹¹ 3305 obese subjects were randomized to lifestyle changes, plus either 120 mg of orlistat or placebo, with a 4-year follow-up. After 4 years

of treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% ($p = 0.0032$). Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; $p < 0.001$). Hollander et al. studied obese patients with non-insulin-dependent diabetes. Orlistat resulted in improved glycemic control (blood glucose and HbA1C), and reductions in total and LDL-cholesterol, triglycerides, and apo-lipoprotein B.¹² These studies show that orlistat not only helps a patient to lose weight but also improves the co-morbid states associated with obesity.

The GI side effects of orlistat, including fatty/oily stool, fecal urgency, oily spotting, increased defecation, fecal incontinence, flatus with discharge, and oily evacuation, are the main reason for discontinuation of therapy. These symptoms are usually mild to moderate and decrease in frequency the longer the medication is continued.

Cavaliere et al.¹³ conducted a study to see if the concomitant use of natural fibers (psyllium mucilloid) would ameliorate the adverse GI events. Subjects who received the psyllium experienced far fewer symptoms. Only 29% of those taking psyllium with orlistat (120 mg tid) had GI events, compared to 71% of patients on placebo.

Subjects who take orlistat can also become deficient in fat-soluble vitamins (vitamins A, D, E, and K); a daily multivitamin is recommended. The usual dose of orlistat is 120 mg, taken orally three times per day with meals. It may be helpful to begin with once-daily dosing, then increase to three times daily if tolerated.

Phentermine

Phentermine is a sympathomimetic anorexigenic agent. It is the most commonly prescribed weight-loss medication in the United States,¹⁴ representing 31% of drug-treated obese patients. Unlike orlistat and sibutramine, which are approved by the FDA for long-term use in the treatment of obesity, phentermine is only approved for up to 3 months of treatment. Use of this medication for greater than 3 months is considered “off-label.” There has only been one randomized, controlled study of phentermine. In that 36-week study, both continuous and intermittent phentermine was found to induce greater weight loss than placebo.¹⁵ The most common side effects of phentermine are insomnia, constipation, and dry mouth. The starting dose is 15 mg daily in the morning, with a maximum of 30 mg.

Other Drugs That Cause Weight Loss

Metformin

Metformin reduces glucose production by the liver and increases insulin sensitivity. Gokcel et al. demonstrated

that metformin achieved similar weight loss to orlistat over a 6-month period.¹⁶ In a placebo-controlled trial of 24 obese, hyperinsulinemic, nondiabetic subjects, met-

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formin was found to be superior to placebo in terms of weight loss ($6.5\% \pm 0.8\%$ versus $3.8 \pm 0.4\%$, $p < 0.01$).¹⁷ Metformin should be the first-line agent in obese diabetic patients. The most common side effects of metformin are nausea, flatulence, diarrhea, and bloating. The most serious side effect, lactic acidosis, is uncommon.

Bupropion

Bupropion is an antidepressant that has been found to induce weight loss, perhaps because of its mechanism as a norepinephrine and dopamine reuptake inhibitor. While the mean weight loss observed with bupropion is small, in some patients bupropion may be preferable to the many other antidepressants that may induce weight gain. Bupropion is contraindicated in patients with epilepsy and may cause anxiety, dry mouth, rash, and, rarely, seizures.

Topiramate

Topiramate is a novel, broad-spectrum antiepileptic agent approved by the FDA (and more than 75 countries) for selected seizure disorders. Topiramate has been found to reduce body weight in patients with a variety of disorders, including epilepsy,¹⁸ bipolar disorder,¹⁹ and binge eating disorder.²⁰ A randomized, double-blind, placebo-controlled, dose-ranging trial was conducted on healthy obese volunteers. At 24 weeks, weight loss in the intent-to-treat analysis (ITT) population was -2.6% for placebo and -5.0%, -4.8%, -6.3%, and -6.3%, respectively, for groups treated with 64, 96, 192, and 384 mg/d ($p < 0.05$).²¹ The most frequent adverse events were related to the central or peripheral nervous system, including paresthesia, somnolence, and difficulty with memory and concentration, as well as renal stones and, rarely, acute angle glaucoma.

Zonisamide

Zonisamide is a second novel antiepileptic associated with weight loss. In a randomized, controlled trial, zonisamide induced significantly more weight loss than

Table 2. Obesity Drugs in Development

Drug Name	Company	Development Status
181771 (CCK-A agonist)	GlaxoSmithKline	Phase II
APD356	Arena Pharmaceuticals	Phase I
Axokine	Regeneron Pharmaceuticals	Phase III
PEGoAxokine	Nektar Therapeutics	Phase I
Peptide YY (3-36)	Nastech Pharmaceutical	Phase I
S-2367	Shionogi	Phase I
SR141716* cannabiod receptor (CB1) antagonist	Sanofi-Synthelabo	Phase III

*Also in development for schizophrenia and smoking cessation (Phase II)

Source: New Medicines in Development. Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, DC. www.phrma.org/.

placebo (mean weight loss $5.8\% \pm 0.8\%$ (6.0%) versus 0.9 ± 0.4 kg (1.0% , $p < 0.001$).²² Fatigue was the only side effect that occurred with a significantly higher fre-

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quency in the treatment group. Other cognitive side effects and, rarely, kidney stones, have been described in epilepsy trials.

Conclusions

Medications have proven efficacy in the management of obesity and its related co-morbid conditions. However, we are still in the early stages of the medical management of obesity. There are many promising medications currently in development that will treat obesity through unique physiological mechanisms (Table 2). Ultimately, obesity will most likely be treated with combinations of medications in a manner similar to the treatment of other chronic diseases, such as diabetes, hypertension, hyperlipidemia, and heart failure. As our understanding of obesity grows, so will our armamentarium to combat this disease. Eventually, the medical treatment of obesity may supplant the treatment of its complications. ■

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