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Weight Loss Drugs: What Works?

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Wanted: A Pill That Melts Fat

As Americans become more obese and the associated health problems reach epidemic proportions, the need for a safe and effective weight loss drug has become urgent. Over the years, this quest has been marked with short-lived triumphs and many defeats, leaving patients and clinicians with less than ideal weapons in the fight against obesity.

The few drugs that have actually reached the market in recent years promote weight loss either by boosting the body's basal metabolic rate, blocking the absorption of dietary fat, or suppressing appetite.People who take these drugs typically lose weight for the first 6 months until they reach a plateau that can't be surpassed without increasing exercise or caloric restriction.The problems with many of these agents have been a lack of proven long-term safety, and the fact that when such drugs are stopped, the weight is usually regained.

Most clinicians are aware that pharmacotherapy is not indicated as a first-line therapy for obesity, and should not be initiated until all nonpharmacologic attempts at weight loss (diet, exercise) have failed.[1] It is also important to evaluate other medications that the patient may already be taking, as some may promote weight gain (eg, sulfonylureas, thiazolidinediones, and insulin), thereby negating the effects of anti-obesity drugs.[2]

The decision to prescribe a weight-loss drug involves a careful assessment of the risks and benefits.[3] As a general rule, an effective regimen should help patients lose at least 4 pounds in the first 4 weeks, or 5% of baseline weight in the first 3 months on therapy.

As researchers continue searching for an ideal weight-loss agent, clinicians must work with available therapies while awaiting newer drugs in the pipeline.

Currently on the Market

Two classes of weight-loss agents are currently available by prescription: noradrenergic agents for short-term weight loss and a lipase inhibitor for long-term weight loss.

Phentermine

Phentermine is US Food and Drug Administration (FDA)-approved for short-term (up to 12 weeks) treatment of obesity and is the most widely prescribed weight-loss drug in the United States.[4] Phentermine

is an adrenergic reuptake inhibitor,[5] stimulating the sympathetic nervous system to release norepinephrine, one of the neurotransmitters involved in modulating food intake. Phentermine suppresses appetite and induces satiety much like amphetamines, but has little effect on dopamine transmission, mitigating its abuse potential.[1] Because its effects last about 12 hours, phentermine should be taken in the morning. When used in combination with diet and exercise, phentermine has produced an average 3.6 kg greater weight loss than placebo.[6]

Phentermine is the relatively "safe half" of the formerly popular (but no longer on the market) weight-loss drug phentermine-fenfluramine (phen-fen). Fenfluramine (but not phentermine) was linked to pulmonary hypertension and valvular heart disease. Phentermine alone was found to be an effective anorectic, and it is still available as a prescription drug in 15 mg to 37.5 mg strengths[7] (although many manufacturers discontinued it).

Adverse effects include irritability, nervousness, restlessness, dry mouth, insomnia, constipation, and headache, but it has also been associated with hypertension, tachycardia, and palpitations, so it should not be taken by patients with cardiovascular disease or significant hypertension. Blood pressure should be monitored during therapy.

Diethylpropion

Like phentermine, diethylpropion is a noradrenergic agent with a similar mechanism of action (releasing and inhibiting the uptake of neurotransmitters norepinephrine and dopamine). Diethylpropion is available in 25-mg standard or 75-mg extended-release formulations, and is approved for short-term treatment of obesity.

In a recent study, 69 obese healthy adults were treated with diet and diethylpropion or diet and placebo.[8] After 6 months, the diethylpropion group lost an average of 9.8% of initial body weight vs 3.2% in the placebo group ($P < .0001$). In 1 year, the mean weight loss in patients taking diethylpropion was 10.6%. Dry mouth and insomnia were the most frequent adverse events.[8]

Benzphetamine and Phendimetrazine

Two other sympathomimetic drugs benzphetamine and phendimetrazine are still available by prescription for short-term weight loss. These drugs also act centrally, releasing dopamine and norepinephrine, resulting in appetite suppression, increased blood pressure, and increased heart rate. As schedule III drugs, however, benzphetamine and phendimetrazine have more potential for addiction and therefore are prescribed less often.[9]

All sympathomimetic drugs stimulate the central nervous system, and can increase blood pressure and heart rate, while releasing glycerol and free fatty acids.[9] Still, in a recent survey of obesity specialists in the United States, these were among the most frequently prescribed drugs in the clinical treatment of obesity. Most respondents (97%) reported prescribing phentermine, 64% prescribed diethylpropion, and 60% prescribed phendimetrazine.[4]

Orlistat

A gastrointestinal and pancreatic lipase inhibitor, orlistat was approved in 1999 as the first in a new class of anti-obesity agents. In the gastrointestinal tract, orlistat binds to gastric and pancreatic lipases, preventing these enzymes from hydrolyzing dietary fat into absorbable free fatty acids.[1] When not absorbed, triglycerides are excreted in the feces, along with cholesterol and fat-soluble vitamins. Taken with meals, orlistat can block the absorption of 30% of ingested fat.[5] In this manner, orlistat reduces caloric intake and may have additional benefits.

A Cochrane meta-analysis[10] of 11 randomized controlled trials of orlistat found that overweight and obese individuals who took orlistat had a mean weight loss of 2.9 kg (2.9%) more than those who took placebo. Compared with placebo, orlistat also significantly reduced waist circumference, body mass index (BMI), blood pressure, fasting glucose, and hemoglobin A1c concentrations in patients with diabetes, as well as total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations.[2]

Adverse effects of orlistat are fairly common, affecting 15%-30% of patients and considered unpleasant and unacceptable by some patients.[2] These include steatorrhea, bloating, fecal urgency, fecal incontinence, and oily stools.[5] Orlistat might also interfere with the absorption of fat-soluble vitamins, including vitamins A, D, E, and K, so it has been suggested that patients taking orlistat should also take a multivitamin supplement containing these micronutrients, at least 2 hours before or after the administration of orlistat.

Concerns about a link between orlistat and colon cancer, as well as possible liver damage, are currently being investigated.[11] Orlistat may also interfere with the absorption, and therefore the effectiveness, of other drugs the patient is taking, such as amiodarone and cyclosporine, and through its effect on vitamin K, it can prolong bleeding in patients taking warfarin.[11] This class of drug should probably be avoided in patients with gastrointestinal disease or malabsorption syndromes.[2]

Orlistat is currently available as a prescription drug (Xenical® 120 mg) or an over-the-counter weight loss supplement (Alli® 60 mg). Although it is approved for long-term weight loss, orlistat's somewhat low tolerability and high cost may limit its long-term use.

Withdrawn or Awaiting Approval

The fall of 2010 was a discouraging time for those who are desperate for a new obesity treatment, including patients who say they would be willing to accept some risk if they were able to lose weight. Hopes were raised and then dashed as promising therapies slipped off the horizon in October, just after an established drug was withdrawn from the market. But companies touting the new therapies are continuing to collect safety information that they hope will satisfy regulators and ultimately allow them to sell their products.

Sibutramine

Abbott, maker of the sibutramine product Meridia®, issued a voluntary product recall in October upon being asked by the FDA to stop marketing Meridia in the United States; this followed reports of an increased risk for heart attack and stroke in Meridia users. Meridia had already been recalled earlier in Canada and Europe.

Sibutramine hydrochloride is a centrally acting monoamine reuptake inhibitor, affecting primarily serotoninand norepinephrine, and to a lesser extent, dopamine.[1] Originally used to treat depression, patients taking sibutramine experienced weight loss as an unexpected effect. Although diminished hunger and increased satiety are the most likely mechanisms of weight loss, sibutramine may also increase thermogenesis, thus increasing energy expenditure by increasing metabolism.[1]

The Sibutramine Cardiovascular OUTcomes (SCOUT) trial was a 6-year study of 10,000 patients, conducted to assess cardiovascular safety in high-risk patients. It showed that, after 5 years (the end of the trial), the average difference in body weight between patients taking Meridia and those taking a placebo was about 2.5%. On long-term follow-up, a 16% increased risk for nonfatal heart attacks and nonfatal strokes was seen in patients with pre-existing cardiovascular risk factors.[12] This was considered by some to be an unacceptable benefit to risk ratio. However, the manufacturer asserts that the increased cardiovascular events occurred primarily in patients with underlying cardiovascular disease, a patient population in whom Meridia is contraindicated according to enhanced labeling initiated earlier this year.[13]

Lorcaserin

Lorcaserin is an anti-obesity drug of the 5-HT_{2C} agonist class. The stimulation of specific central serotonin receptors suppresses appetite and induces a feeling of satiety. Lorcaserin is highly selective for the 5-HT_{2C} receptor, which modulates fat and caloric intake.[14] Signaling through the 5-HT_{2A} and 5-HT_{2B} receptors (found on cardiac valves), however, is minimal.[2]

In a large trial (3182 patients), those who took lorcaserin lost an average of 5.8% of their baseline body weight compared with 2.2% in those who took placebo ($P < .001$).[15] Nearly half of the patients taking lorcaserin lost 5% or more of their baseline body weight, compared with 20% of those taking placebo, and more of the lorcaserin patients maintained their weight loss after the study had ended. Very few patients in

the lorcaserin group failed to lose weight.

Other improvements associated with lorcaserin were: reduced BMI and waist circumference; lower fasting glucose, insulin, and A1c levels; and lower total cholesterol, LDL cholesterol, and triglycerides. However, despite beneficial effects on risk for cardiovascular disease (reduced C-reactive protein, fibrinogen level, systolic and diastolic blood pressure, and heart rate), the FDA voted against approval of lorcaserin in October, citing concerns about lorcaserin-induced valvular heart disease (as well as brain and breast tumors) in declining to recommend lorcaserin for the treatment of obesity.[16]

The agency requested additional data about lorcaserin from drug maker Arena Pharmaceuticals, and the company says it will meet with the FDA before the end of the year, partly to discuss new, "encouraging" data regarding lorcaserin's effects on obese patients with diabetes.

Phentermine/Topiramate

Qnexa® (made by Vivus, Inc.) combines low-dose phentermine with a controlled-release form of topiramate, an antiepileptic drug often used for the prevention of migraine headache. Topiramate inhibits excitatory neurotransmissions by blocking voltage-gated sodium channels,[17] and is sometimes prescribed as monotherapy for weight loss.[4] Topiramate reduces hunger and promotes weight loss in a dose-dependent fashion, but the peripheral and central nervous system effects (parasthesias, memory impairment, taste disturbance) are significant and intolerable in some patients.[18] Topiramate has the added advantage of having mood-stabilizing properties.[5]

Harnessing the effects of the 2 different but complementary mechanisms of phentermine and topiramate allows the use of lower doses of each agent, which should increase safety.[19] This drug combination reportedly induces substantial weight loss, an average of about 10% after 1 year, and significantly reduces systolic blood pressure. Patients taking lower doses of the drug combination lose less weight, but that is still more than those taking placebo.

Despite evidence of effectiveness in phase 3 trials extending to 1 year, the FDA voted against approval of Qnexa in October, expressing concerns about adverse effects associated with its use, including cognitive disorders, metabolic acidosis, increased heart rate, and birth defects, suggesting possible teratogenicity.

Before Qnexa can be approved, the FDA has requested further evidence of its safety.[19] If approved, it would be a schedule IV drug due to the phentermine component.

Naltrexone/Bupropion

Contrave®, another new dual anti-obesity agent, is the combination of the antidepressant bupropion and sustained-release (SR) naltrexone, a drug used to treat alcoholism and other addictions. Bupropion, approved for both depression and smoking cessation, also increases dopamine levels at specific receptors in the brain, which is believed to be responsible for its appetite-reducing effects.[20] These 2 drugs work on the brain reward system and the hunger centers in the hypothalamus, and are believed to be synergistic in reducing food intake.[21]

If approved, this combination therapy could be useful for patients who have issues with food craving. When used with a mild hypocaloric diet and with exercise instruction in overweight or obese patients, it is associated with greater weight loss and greater improvement in several cardiometabolic risk factors compared with placebo.[22] Combination treatment was generally well tolerated; adverse effects included insomnia, nausea, headache, dry mouth, and a small and transient increase in systolic and diastolic blood pressure.[22]

Contrave has not yet been reviewed by the FDA, but phase 3 clinical trials have been completed. The manufacturer, Orexigen, reports that Contrave met all of its primary endpoints for weight loss in these trials, even in patients with diabetes, it also was associated with improvements in cardiometabolic risk markers such as waist circumference, HDL-C levels, and triglyceride levels.[23] Contrave is up for review by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee in December 2010.[23]

The fate of this anti-obesity agent will not be known until sometime in 2011.

In the Pipeline

Zonisamide / Bupropion

In clinical trials for the relatively new antiepileptic zonisamide, an unanticipated effect was weight loss. It has, therefore, been studied for its potential as a weight-loss agent, either in monotherapy or in combination with other agents such as bupropion. Zonisamide has sodium and calcium channel blocking activity, as well as dose-dependent biphasic dopaminergic and serotonergic activity. Empatic™ (made by Orexigen) is a fixed-dose combination of a proprietary formulation of zonisamide SR and bupropion SR.

In trials at Duke University, zonisamide alone with a hypocaloric diet was shown to be more effective in reducing weight than placebo.[24] The same investigators have conducted a short-term, open-label trial of treatment with zonisamide and bupropion, finding that the combination resulted in more weight loss than zonisamide alone.[25] Fatigue, drowsiness, sedation, nausea, and cognitive impairments (difficulty concentrating, memory problems, speech and language difficulties) have all been reported with zonisamide use.[25]

The manufacturer of Empatic recently reported that in phase 2b trials, patients who took the drug for 24 weeks lost 9.9% of their baseline body weight compared with 1.7% for patients taking placebo, without evidence of a plateau. Improvements in waist circumference, triglycerides, fasting insulin, and blood pressure were also reported.[23] Phase 3 trials are now planned.

Tesofensine

Tesofensine (made by NeuroSearch) is a triple monoamine reuptake inhibitor that blocks the presynaptic uptake of norepinephrine, dopamine, and serotonin.[17] Originally being studied for neurodegenerative conditions such as Parkinson and Alzheimer diseases, unintended weight loss was observed in individuals treated with the drug.[26]

The mechanisms through which tesofensine leads to weight loss are a pronounced effect on appetite suppression and increased energy expenditure.[27] In phase 2 clinical trials with tesofensine in obese patients, dose-related reductions in body weight, body fat, and waist circumference, as well as improvements in other obesity-related measures, were observed. Minor adverse events included elevations in heart rate and significant increases in blood pressure only at the highest tested dose.[28] The drug is soon to be tested in phase 3 clinical trials.[26]

Cetilistat

Cetilistat is a new lipase-inhibitor with a similar mode of action to orlistat, inhibiting pancreatic lipase and blocking digestion and absorption of dietary fat, so that it can be eliminated unchanged with the stool. Cetilistat has completed a 12-week phase 2b trial in obese patients, demonstrating weight loss consistent with other obesity medications and significant improvements in other obesity-related parameters.[29] Unpleasant adverse effects, including flatus with discharge and oily spotting, were reported by fewer than 3% of patients using cetilistat.

It is probable that, like orlistat, cetilistat will also block the absorption of fat-soluble vitamins, and this possibility was raised by the FDA in 2009, cautioning that cetilistat could "lead to malabsorption of nutrients and vitamin deficiency."[30] Cetilistat has now been cleared to conduct phase 3 trials in patients with obesity.

Pramlintide / Metreleptin

The combination of these 2 agents represents a novel integrated neurohormonal approach to obesity.[31] Pramlintide is an analogue of amylin, a hormone secreted by pancreatic beta cells along with insulin. Exogenous amylin can increase the absorption of glucose, slow gastric emptying, and by binding to hypothalamic receptors, promote satiety, reduce food intake and elicit weight loss. Metreleptin is recombinant methionine human leptin. Leptin is a neurohormone secreted by adipocytes that also binds to receptors in the hypothalamus to promote satiety. When someone reduces dietary intake to lose weight, leptin levels drop, and this triggers a host of counter-regulatory responses aimed at maintaining body

weight. Administration of metreleptin restores leptin concentrations and attenuates the effects of counter-regulation.[31]

Pramlintide is already an approved drug in the treatment of diabetes. Metreleptin has been tested as monotherapy for obesity/weight loss, but failed because of the development of leptin resistance. However, these 2 hormones are believed to act synergistically to reduce food intake and body weight.

Mildly and moderately obese patients (without diabetes) who took this combination lost about 13% of baseline body weight in 24 weeks with no weight-loss plateau, significantly more than was seen with either drug administered as a single agent. Patients who continued treatment with pramlintide/metreleptin for a total of 52 weeks exhibited sustained weight loss, whereas those who received placebo during the extension study regained almost all of their lost weight. The combination therapy appeared to be generally well tolerated. The most common adverse effect was nausea.[31]

Pramlintide/metreleptin combination is an injectable therapy, which may limit its application in the general obese population.

Potential Future Therapies

ZGN-433, a methionine aminopeptidase inhibitor, targets the adipose tissue rather than the central nervous system. This class of medication essentially works by restoring control of adipose tissue lipolysis, ketogenesis, food intake, and fat synthesis. ZGN-433 is believed to stimulate adipose tissue to convert stored triglycerides into free fatty acids that can be used for energy.[32]

ZGN-433 is still in the early stages of development but has shown promise in rodent studies. A safety and tolerability study in humans is in progress.

Another novel therapy that may have a role in weight loss is ezlopitant, a neurokinin receptor-1 (NK1R) antagonist. The NK1R system has been implicated in both learned appetitive behaviors and addiction to alcohol and opioids; recent evidence from rodent studies suggests that ezlopitant reduces the appetite for sucrose as well, thus decreasing the consumption of sweetened foods and drinks.[33] It has been suggested that sweet foods and drinks can be addictive in the same way as alcohol, explaining the suppressant effects of ezlopitant.

The antidiabetes drugs represent another possible drug class to mine for potential weight-loss effects and for possible development as dual diabetes/obesity agents. Metformin, a biguanide approved for the treatment of type 2 diabetes, causes weight loss by reducing hepatic glucose production and intestinal absorption from the gastrointestinal tract, and enhancing insulin sensitivity.[34]

Liraglutide (Victoza®), another drug that is already approved for the treatment of type 2 diabetes, induces moderate weight loss of approximately 2-3 kg.[35] The glucagon-like peptide-1 (GLP-1) receptor agonists exenatide and liraglutide are newer medications for diabetes that have favorable effects not only on glycemic control but also on weight loss.[3] Although some of these agents might not induce enough weight loss to qualify as anti-obesity agents, they could prove useful for overweight individuals who have diabetes.[34]

Final Thoughts on Anti-Obesity Pharmacotherapy

Obesity is a chronic, relapsing, biologic condition that may well require long-term pharmacotherapy, in the same manner as hypertension and diabetes. To date, however, the average amount of weight lost with most pharmacologic agents has been modest at best, and the typical patient will most likely remain overweight or obese even with ongoing treatment.[12]

Weight-loss drugs are expensive; neither Medicare nor most insurance plans cover them. In addition, most are associated with adverse effects. Therefore, meeting efficacy criteria for weight loss is not good enough for anti-obesity agents that will be taken by millions of people for many years. The benefits of any weight-loss drug must outweigh the risks, and safety is the overriding consideration.

It is too early to tell whether some of the novel weight loss drugs still in development will offer greater efficacy and safety. What is certain is that drug developers will continue to search for the Holy Grail of anti-obesity drugs as the world's girth continues to expand.

The Weight-Loss Imperative

The classifications of "overweight" and "obese" are defined by BMI, calculated from a patient's weight and height. A person with a BMI ≥ 25 kg/m^2 is considered "overweight" and someone with a BMI ≥ 30 k/m^2 is considered, "obese." Using these definitions, 68% of the adults in the United States are overweight, and 34% are obese.[36]

The days when obesity was considered primarily a cosmetic problem are long gone. We now know that obesity is a complex disease that develops from a combination of genetic and environmental factors, and that the health implications of obesity are vast (see Table). In addition to elevated rates of type 2 diabetes, cardiovascular disease, and cancer, obesity can make surgical management more difficult and result in more postoperative complications.[37,38]

Evidence of a survival benefit for obesity in select clinical situations is not enough to compensate for the overwhelming health risks, including death, associated with excessive body weight.[4]

Table. Diseases Associated With Obesity[39]

Organ System	Conditions
Cardiovascular	Hypertension, peripheral vascular disease, myocardial infarction, cerebral vascular accidents, peripheral venous insufficiency, thrombophlebitis, pulmonary embolism
Respiratory	Asthma, obstructive sleep apnea, obesity-hypoventilation syndrome
Metabolic	Type 2 diabetes mellitus, impaired glucose tolerance, hyperlipidemia
Musculoskeletal	Back strain/disc disease, osteoarthritis
Gastrointestinal	Cholelithiasis, gastrointestinal reflux disease, nonalcoholic fatty liver disease, hepatic cirrhosis, hepatic carcinoma, colorectal carcinoma
Urologic	Stress incontinence
Endocrine/Reproductive	Polycystic ovary syndrome, pregnancy/fetal abnormalities, male hypogonadism, endometrial, breast, ovary, prostate cancer, pancreatic cancer
Dermatologic	Intertriginous dermatitis
Neurologic	Pseudotumor cerebri, carpal tunnel syndrome
Psychologic	Depression, eating disorders, body image disturbance

Clinical Interventions for Obesity

The chief clinical intervention for obesity is lifestyle change, which usually involves counseling and behavioral therapy for reducing caloric intake and increasing physical activity. For patients who fail to lose weight with lifestyle intervention, pharmacotherapy and surgical approaches may be indicated.

The benefits of weight reduction, even on a fairly modest scale (5%-10% of body weight) are well documented. Among other benefits, weight loss is associated with a lower incidence of diabetes, hypertension, and dyslipidemia,[40] improved urinary incontinence,[41] and reduced inflammation in osteoarthritis.[42] Patients with diabetes who lose even small amounts of weight have better metabolic control, fewer cardiovascular risk factors, and lower mortality rates.[43,44] Continually losing and regaining weight (weight cycling), however, might be worse than maintaining a stable excessive weight. The evidence on weight cycling and threats to health is inconsistent, but raises the question of its safety.[45]

Unfortunately, the degree of weight loss that is usually achieved with lifestyle intervention alone is insufficient. Efforts to lose weight are often thwarted by a compensatory slowing of the metabolism and high rates of recidivism.[2]

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