

## Review Article

# Present and Future: Pharmacologic Treatment of Obesity

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Obesity now presents one of the biggest health problems of our times. Diet and exercise are best for both prevention and treatment; unfortunately, both require much discipline and are difficult to maintain. Medications offer a possible adjunct, but their effect is modest, they are limited by side effects, and the weight loss lasts only as long as the drug is being taken, since as soon as treatment is stopped, the weight is regained. Sibutramine, a sympathomimetic medication which was available for long-term treatment, is the most recent of the drugs to be withdrawn from the market due to side effects; in this case it was an increased risk of cardiovascular events. This paper reviews those medications which are available for treatment of obesity, including many of those recently taken off the market. It also discusses some of the newer treatments that are currently being investigated.

## 1. Introduction

Obesity has become one of the biggest health problems of our times. The World Health Organization's (WHO) latest projections indicated that globally in 2005 approximately 1.6 billion adults were overweight and at least 400 millions were obese. The WHO further projects that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese. At least 20 million children younger than 5 years old were overweight in 2005 [1].

Although obesity has been labeled a disease for over 200 years [2], only recently has it been recognized as a condition that warrants medical attention. This is especially true given the mounting data on the correlation between obesity and type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, stroke, and depression. Obesity is associated with osteoarthritis, obstructive sleep apnea, increased risk of cancer, and nonalcoholic fatty liver disease. It is related to a variety of other complications, such as gastrointestinal reflux disease, gout, headache, cellulitis, chronic renal failure, hypogonadism, and erectile dysfunction, among others. Moreover, obesity is associated with a reduced quality of life and social stigmatization [3, 4]. Unfortunately, doctors remain reluctant to bring up the topic of obesity when seeing

patients in their clinic. Less than 50% of obese patients are even advised to lose weight [5].

This low involvement on the part of the doctor may be due, in part, to the fact that at this time there is still no magic bullet for the treatment of obesity, and diet and exercise continue to be the cornerstone of treatment. Given the frustrations doctors and patients face in achieving results by diet and exercise, drug therapy offers an attractive option, even if the results are modest. Unfortunately, despite the frantic search at the moment for pharmacotherapy, few options currently exist. In the last few years many drugs that have been effective weight loss medications have had to be withdrawn from the market secondary to unacceptable side effects. Fen-Phen, which was marketed as a combination of two drugs fenfluramine and phentermine, was removed from the market in September 1997, after it was reported that it could cause valvular heart disease and pulmonary hypertension [6]. In 2000, phenylpropanolamine, an over-the-counter weight loss drug, was found to be an independent risk factor for hemorrhagic stroke in women [7]. The first selective CB1 receptor blocker, Rimonabant, was never approved in the USA, but was available in 56 countries from July 2006 to January 2009, when it was withdrawn from the European market due to the fact that it caused increased depression

and suicidal ideation [8]. More recently, in October 2010, sibutramine, a centrally acting serotonin-norepinephrine reuptake inhibitor structurally related to amphetamines, was withdrawn from the market because of its association with increased cardiovascular events and strokes [9].

This paper reviews those medications which are available for treatment of obesity, including many of those recently taken off the market. It will also discuss some of the newer treatments that are currently being investigated. While bariatric surgery has been increasing in popularity, and certainly offers a powerful tool with which to treat obesity, it is beyond the scope of this paper.

## 2. Indications for Medical Therapy

Obesity is defined as a body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) of 30 or more. Clinical practice guidelines for the pharmacologic and surgical management of obesity in primary care have been issued by the American College of Physicians (ACP) [10]. These guidelines are based upon the results of two meta-analyses [11, 12] and the existing guidelines from the United States Preventive Services Task Force.

The guidelines include five recommendations. (1) Counsel all obese patients ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) on diet, lifestyle, and goals for weight loss. (2) Pharmacologic therapy may be offered to those who have failed to achieve weight loss goals through diet and exercise alone. (3) Pharmacologic options include sibutramine, orlistat, phentermine, diethylpropion, and two drugs that are not approved for obesity treatment, fluoxetine and bupropion. (4) Bariatric surgery should be considered for patients with  $\text{BMI} \geq 40 \text{ kg/m}^2$  who have failed diet and exercise (with or without drug therapy) and who have obesity-related comorbidities (hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea). (5) Bariatric surgery should be performed at high-volume centers with experienced surgeons. The NIH also suggests that weight loss drugs approved by the Food and Drug Administration (FDA) for long-term use can be used or for patients with a BMI of  $\geq 27$  accompanied by risk factors or diseases. These risk factors are hypertension, dyslipidemia, coronary heart disease, type 2 diabetes, and sleep apnea [13]. These recommendations may possibly change soon, in light of the new findings linking sibutramine to an increased rate of cardiac events [9]. The NIH also suggests that adults with a BMI  $> 35$  who have serious comorbidities such as diabetes, sleep apnea, obesity-related cardiomyopathy, or severe joint disease may also be candidates for bariatric surgery [14].

## 3. Goals of Therapy

Perhaps the most important aspect of starting pharmacological treatment for obesity is to set realistic goals. Given the difficulties of dieting, it is nearly impossible to reach the patients expectations. Numerous studies have shown that obese individuals want to lose the equivalent of 25–35% of their initial weight and expect to do so in approximately 1 year of treatment [15]. Dieters maintain these expectations

even when repeatedly informed that they are likely to lose only 5–15% of initial weight, which is the size of the losses typically induced by current behavioral and pharmacological interventions [16]. These data illustrate the dramatic disparity between patients' expectations and professional recommendations and the need to help patients accept more modest weight loss outcomes. A realistic treatment goal is usually the loss of 5–10% of initial body weight over a 6- to 12-month period, followed by long-term maintenance of reduced weight. The NIH guidelines recommend that weight loss should exceed 2 kg during the first month of drug therapy (1 pound per week), fall more than 5% below baseline by three to six months, and remain at this level to be considered effective [17]. If this is not achieved, then the dose should be adjusted or the medication discontinued.

Although weight loss is an important treatment outcome, a major goal of obesity management should be to improve cardiovascular and metabolic risk factors in order to reduce obesity-related morbidity and mortality. Modest weight loss as low as 5% of initial body weight can lead to favorable improvements in blood pressure, serum lipid concentrations, increased insulin sensitivity, and improved glucose levels [18–21]. Patients who have impaired glucose tolerance, type 2 diabetes, or hypertension are the ones who benefit the most as far as improvement in cardiovascular risk factors [22]. The ongoing Look AHEAD study, initiated in 1999, is a 12-year prospective trial designed to determine whether a 7% weight loss will reduce the occurrence of myocardial infarction and stroke in overweight patients who already have type 2 diabetes [23].

When starting pharmacological therapy it is important that the patient understands that once the maximal therapeutic effect is achieved, weight loss plateaus and that when drug therapy is discontinued, the weight is regained [17]. Because the body reduces its energy expenditure as it loses weight, more and more effort must be made to maintain the weight loss [24]. Weight regain results from complex interactions between multiple factors including physiologic, environmental, and psychological factors. Physiologic factors include reduced metabolic rate, both resting and nonresting [25, 26], and increased adipose tissue lipoprotein lipase activity [27]. These counterregulatory mechanisms protect against starvation by causing an increase in appetite and a decrease in energy expenditure, making it very difficult to keep off the weight that was lost.

Patients must also be made aware of the fact that the data on the use of these medications is limited, given that the longest trials for sibutramine have a duration of only two years, and for orlistat a maximum of four years. The trials for the remaining medications are even shorter. Therefore, if there is a good response to the medication and the patient wishes to continue, the decision should be a shared discussion between the physician and patient.

## 4. Review of Medications

**4.1. Orlistat-Lipase Inhibitor.** Orlistat (Xenical) was approved in 1998 for use for more than 12 weeks, which is considered a long-term use. It reduces dietary fat absorption

by 30% by inhibiting pancreatic and gastric lipase [28]. Orlistat is available in 120 mg capsules. The recommended dose is 120 mg three times daily. A lower dose (60 mg), which is not as effective, is available over-the-counter in some countries, including the United States.

Three randomized, double-blind, placebo-controlled trials of orlistat lasting two years have been published. These showed that orlistat 120 mg (three times/day), taken with an appropriate diet, resulted in clinically significant weight loss and reduced weight regain when compared to placebo. The orlistat group, on average, lost 10.2% versus placebo which lost 6.1% of body weight ( $P < .001$ ) from randomization to the end of the first year. During the crossover portion of the study in the second year, patients who continued with orlistat regained, on average, half as much weight as those patients switched to placebo ( $P < .001$ ) [28–30].

In a longer four-year study involving 3305 obese patients, 21% of whom had impaired glucose tolerance, orlistat led to weight loss during the first year of more than 11% below baseline in the orlistat-treated group versus 6% in the placebo-treated group [31]. Over the remaining years of the trial, both groups regained weight, but overall, the orlistat-treated patients were 6.9% below baseline, compared with 4.1% for those receiving placebo.

In a meta-analysis of 22 trials that included patients with and without diabetes and reported data with 12-month outcomes, the mean difference in weight loss due to orlistat was  $-2.89$  kg ( $-3.51$  to  $-2.27$  kg) [11]. With an average placebo effect of  $-5.5$  kg, this translates into an expected loss of  $-8.83$  kg on average for patients who adhered to the treatment for this long. Almost two-thirds of the subjects completed the first year of treatment. Weight loss at one year varied from 5.5 to 6.6% of initial body weight in the placebo groups and 8.5 to 10.2% in the orlistat groups. Also in diabetic patients orlistat resulted in significantly more weight loss and a decrease in hemoglobin A1c at one year than placebo [32–34]. In all the studies, the lowest body weight was achieved during the first year.

The moderate effect on body weight is sufficient to improve several metabolic parameters. In a multicenter trial, as an example, serum total and LDL cholesterol concentrations both decreased by 4–11% in subjects treated with a weight-maintaining diet plus 30 to 360 mg of orlistat per day for eight weeks [35]. Blood pressure was reduced by 1.8 mmHg systolic and 1.6 mmHg diastolic. A retrospective analysis showed reductions in triglyceride and cholesterol blood levels, improved oral glucose tolerance, and a fall in systolic and diastolic blood pressure [30].

The major side effects of orlistat therapy are gastrointestinal, including intestinal cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge [34]. These occur in 15–30% of the patients and tend to occur early and to subside as patients learn how to avoid high fat diets and stick to the recommended intake of no more than 30% fat. Levels of fat-soluble vitamins (A, D, E) and beta-carotene are reportedly lowered by orlistat therapy, with vitamin D the most frequently affected; therefore it seems prudent to also give a multivitamin supplement when prescribing orlistat [34].

*4.2. Sibutramine-Sympathomimetic Drug, Formerly Approved for Long-Term Use.* Sibutramine (Meridia, Reductil) was first developed as an antidepressant, and although it was ineffective for this, it was found to reduce body weight and appetite. It is a centrally acting noradrenaline and serotonin reuptake inhibitor that enhances weight loss by increasing satiety. It may also have a thermogenic effect in human beings, but this remains controversial. It is given as a 10 mg dose once daily, usually in the morning, and could be increased to 15 mg daily after 4 weeks if needed. It was available from 1997 until October 2010. We will discuss the side effects that led to its withdrawal, but first we will review its efficacy.

More than 10 prospective, randomized, controlled trials of sibutramine lasting 6–24 months have supported its efficacy [11]. 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; 34% more patients achieved at least 5% weight loss, and 15% more patients achieved at least 10% weight loss in the sibutramine arm compared with placebo [36]. The weight loss seems to be dose dependent [37], and the extent of initial weight loss in subjects treated with sibutramine predicts the long-term response. In two different weight maintenance trials comparing sibutramine to placebo, more weight loss was seen in the drug-treated patients (mean 5.2 kg) while the placebo group gained weight (mean 0.5 kg) [38, 39].

There are benefits to using sibutramine intermittently, as was seen in a randomized, placebo-controlled trial lasting 52 weeks [39]. The patients received either continuous treatment with sibutramine at 15 mg/day for 1 year or sibutramine with two 6-week periods when the drug was withdrawn. During the periods when the drug was replaced by placebo, there was a small regain in weight that was again lost when the drug was resumed. At the end of the trial, the continuous-therapy and intermittent-therapy groups had lost the same amount of weight.

Another study highlights how much intense lifestyle modification contributes to the success of medical treatment. In a 1-year randomized trial, 224 obese adults received sibutramine alone, sibutramine plus brief individualized lifestyle modification (8–10 visits of 10–15 min each), group lifestyle modification alone (30 sessions), or sibutramine plus 30 sessions of group lifestyle modification [40]. All subjects were prescribed a calorie-restricted diet of 1200 to 1500 kcal per day and the same exercise regimen. At one year, subjects in the combined therapy group lost a mean of  $12.1 \pm 9.8$  kg, while those receiving sibutramine alone, lifestyle modification alone, or sibutramine plus brief lifestyle intervention counseling lost  $5.0 \pm 7.4$  kg,  $6.7 \pm 7.9$  kg, and  $7.5 \pm 8.0$  kg, respectively.

A number of studies have demonstrated that obese patients with diabetes also seemed to benefit from sibutramine therapy [41–44]. As an example, in a six-month trial in patients with diabetes, those treated with sibutramine lost weight and had a decline in hemoglobin A1C values, but no change in blood pressure [42]. In a meta-analysis of eight randomized trials in 1093 obese patients with type 2 diabetes, significant decreases were noted in body weight,

waist circumference, fasting blood glucose, and HbA1C in the sibutramine group compared to placebo. Other treatment benefits included decreased serum triglycerides and increased HDL concentrations [44].

In all these trials weight loss is associated with improved lipid profiles [41, 42, 44]; however, the data for blood pressure has been conflicting. In many trials patients treated with sibutramine had significant, albeit small, changes in blood pressure [45, 46], on average by 1 to 3 mmHg. This includes patients with hypertension controlled with other agents, such as calcium-channel blockers with or without concomitant thiazide treatment [47]. However, a large surveillance study of 6360 patients suggested a significant decrease in blood pressure with sibutramine in obese hypertensive patients [48].

The different trials also show that a small, but significant increase in pulse rate is seen with sibutramine use. In a systematic review of 29 trials, the mean increase in heart rate with sibutramine was 3.76 beats/min (95% confidence interval, 2.70–4.82 beats/min) [47]. None of the antihypertensive drugs, including beta-blockers, appear to prevent the rise in pulse rate with sibutramine.

Uncertainties about the cardiovascular safety of sibutramine led to the initiation of the randomized, double-blind, placebo-controlled Sibutramine Cardiovascular Outcomes Trial (SCOUTs), which is the longest and largest study with sibutramine [49]. This recently published study enrolled nearly 10,000 patients who were followed for a mean of 3.4 years. It was designed to determine the impact of weight loss with sibutramine on cardiovascular problems in a population already at high risk for cardiovascular disease, with 60% of the patients having a history of cardiovascular disease and diabetes. The primary endpoint was the time from randomization to the first occurrence of a primary outcome event, which included nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death. All patients were first in a 6-week lead-in period with sibutramine, in which the mean weight loss was 2.6 kg. The subjects were then randomized to sibutramine or placebo. The subjects in the sibutramine group then achieved a further weight loss of 1.7 kg, while the placebo group gained weight, an average of 0.7 kg by month 12. The mean blood pressure decreased in both groups, with greater reductions in the placebo group than in the sibutramine group (mean difference, 1.2/1.4 mmHg). The trial showed that the risk of a primary outcome event was increased by 16% in the sibutramine group as compared with the placebo group (hazard ratio, 1.16; 95% confidence interval (CI), 1.03 to 1.31;  $P = .02$ ), with overall incidences of 11.4% and 10.0%, in the two groups, respectively. The rates of cardiovascular death and death from any cause were not increased. Due to these findings, where the weight loss did not seem to outweigh the cardiovascular risks, the European Medicines Agency recommended the suspension of marketing authorizations for sibutramine across the EU. Months later, due to pressures exerted by the FDA, Abbot Laboratories announced that it too would withdraw sibutramine from the US market [50].

**4.3. Benzphetamine, Diethylpropion, Phendimetrazine, and Phentermine-Sympathomimetic Drugs Approved for Short-Term Treatment.** Benzphetamine (Didrex), Diethylpropion (Tenuate), Phendimetrazine (Bontril), Phentermine (Adipex-P), and Mazindol (Mazanor, Sanorex) are approved for use for a period of up to 12 weeks. They are all amphetamine derivatives that lead to weight loss by suppressing appetite. Like amphetamines, they are centrally acting medications that increase blood pressure and pulse rate. Of these, phentermine is the most frequently prescribed weight loss medication [51]. Phentermine comes in 15 mg, 30 mg, and 37.5 mg doses and should be given once daily. Tablets may be divided in half, and dose may be given in 2 divided doses, while avoiding late evening administration.

Phentermine administered continuously in a 36-week double-blind trial in 108 women led to 12.2 kg loss, versus placebo which was 4.8 kg [52]. Diethylpropion has been around since the 1950s, but up until very recently it had rarely been studied beyond 20 weeks. However, a recent randomized double-blind placebo-controlled study lasting for one year showed that diethylpropion was safe. In the study, 69 obese healthy adults received a hypocaloric diet and were randomized to diethylpropion 50 mg BID or placebo for 6 months. After this period, all participants received diethylpropion in an open-label extension for an additional 6 months. After 6 months, the diethylpropion group lost an average of 9.8% (s.d. 6.9%) of initial body weight versus 3.2% (3.7%) in the placebo group ( $P < .0001$ ). From baseline to month 12, the mean weight loss produced by diethylpropion was 10.6% (8.3%). Participants in the placebo group who were switched to diethylpropion after 6 months lost an average of 7.0% (7.7%) of initial body weight. The difference between groups at month 12 was not significant ( $P = .07$ ). There was no difference between the two groups with respect to cardiovascular and psychiatric side effects [53].

Phentermine and diethylpropion have been shown to reduce weight significantly when used intermittently. In a way, this means that they can be used as chronic medications, as long as they are used in alternating months, and therefore still remaining within the short-term limitations [52]. Phentermine and diethylpropion are classified by the U.S. Drug Enforcement Agency as schedule IV drugs, meaning that they have a very low potential for drug abuse. Benzphetamine and phendimetrazine are schedule III drugs, meaning that they have a slightly higher potential for abuse; however, this potential appears to be very low.

## 5. Diabetes Medications That Lead to Weight Loss

The increased weight associated with many commonly prescribed antidiabetic medications such as insulin, sulfonylureas, and thiazolidinediones leads many doctors and patients to resist intensifying therapy as needed [54]. Fortunately not all medications cause weight gain, and recently new medications have been introduced that actually cause weight loss.

**5.1. Metformin.** Metformin (Glucophage) was first investigated for its effects on weight loss in trials as early as 1969 [55], but though the results were promising, metformin was put aside when the following year a trial comparing metformin with fenfluramine showed that fenfluramine was much more effective. Since then, only 9 trials have evaluated weight loss as a primary endpoint of metformin treatment. All of these studies, sometimes combined with orlistat or sibutramine, showed significant weight reduction, but they were short-term studies, consisting of no more than 50 patients each [56–59].

Metformin comes in doses of 500 mg, 850 mg, or 1000 mg. Generally, clinically significant responses are not seen at doses <1500 mg daily; however, a lower recommended starting dose and gradual increased dosage are recommended to minimize gastrointestinal symptoms. Extended release formulations are available.

There are few large randomized controlled trials evaluating the effect of metformin on weight as a secondary outcome. The largest one is the Diabetes Prevention Program [60]. This was a large-scale trial involving 3234 patients with impaired glucose tolerance, which primarily evaluated the incidence of diabetes at the end of the treatment period among patients treated with either metformin, standard lifestyle intervention (placebo group), or intensive lifestyle modification. After an average of 2.8 years of follow-up, the metformin-treated group lost 2.5% of their body weight over placebo ( $P < .001$ ).

The BIGPRO (Biguanides and Prevention of the Risks in Obesity) trial evaluated the relationship between insulin resistance and cardiovascular disease by giving metformin to insulin-resistant patients [61]. The preliminary stage was reported in the BIGPRO1 trial, which randomized 324 patients to receive metformin 850 mg daily or placebo. The metformin-treated patients had a nonsignificant decrease in weight after 1 year ( $-2$  kg in metformin versus  $-0.8$  kg in placebo) ( $P < .06$  versus placebo). Significant differences were observed for systolic blood pressure, which decreased considerably more with metformin versus placebo ( $P < .003$ ), and for fasting plasma glucose and total and LDL cholesterol, which decreased slightly with metformin, while increasing with placebo ( $P < .04$ ;  $P < .02$  for LDL cholesterol). There was also a (nonsignificant) trend towards a greater reduction of diastolic blood pressure in the metformin group ( $P < .09$ ), whereas weight, BMI, waist-to-hip ratio, 2 hPG, fasting and 2-h insulin, HDL cholesterol, triglycerides and fibrinolytic markers did not differ between the two treatment groups [62].

The most common side effects of metformin are gastrointestinal, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements, or diarrhea. Lactic acidosis is an uncommon side effect; however, it remains a concern because of the high case fatality rate. Thus, metformin should not be administered to individuals with predisposing factors for developing lactic acidosis, such as those with impaired renal function.

**5.2. GLP-1 Agonists: Exenatide and Liraglutide.** GLP-1 is a hormone secreted by L cells in the terminal ileum after food intake. It decreases blood glucose by inhibiting glucagon secretion and stimulating insulin secretion. GLP-1 also delays gastric emptying, reduces caloric intake, and promotes satiety. Exenatide (Byetta) is a GLP-1 receptor agonists that shares 53% homology to GLP-1 and has a much longer half life because it is resistant to dipeptidyl peptidase-4- (DPP-4-) mediated degradation. It is administered as a subcutaneous injection twice daily. It is approved to treat type 2 diabetes and produces similar effects to GLP-1, reducing fasting and postprandial glucose levels, decreasing HbA1c, slowing gastric emptying, and decreasing food intake by about 19%. In diabetic patients it has been shown to cause weight loss by an average of 1.6 kg without any change in lifestyle, diet, or exercise [63].

Exenatide, available in prefilled syringes that hold a month's supply of either 5 or 10 mcg doses, is administered subcutaneously twice daily immediately before or within one hour of morning and evening meals [64]. Exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage kidney disease.

A study that followed 314 overweight patients with type 2 diabetes, the first 30 weeks of which were double blind, followed by an open-label observation to week 82, showed progressive weight reduction in 80% of patients, with an average reduction of 4.4% body weight [65]. Recently another study was published that assessed the effects of exenatide on body weight and glucose tolerance in 152 nondiabetic obese subjects with normal or impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) [66]. They were randomized to receive exenatide or placebo, along with lifestyle intervention, for 24 weeks. The exenatide-treated subjects lost  $5.1 \pm 0.5$  kg from baseline versus  $1.6 \pm 0.5$  kg with placebo ( $P < .001$ ), with a placebo-subtracted difference in percent weight reduction of  $-3.3\% \pm 0.5\%$  ( $P < .001$ ). IGT or IFG normalized in 77% and 56% of exenatide and placebo subjects, respectively. Exenatide offers a good alternative for weight loss, particularly in nondiabetic obese subjects with glucose intolerance.

A once a week version of exenatide is currently being tested, so far, only in diabetic patients. The DURATION-1 study evaluated the safety and efficacy of treatment with the exenatide once weekly (2 mg) compared to exenatide twice daily in 295 patients with type 2 diabetes. It appears that once a week exenatide will be just as effective as twice daily injections, since at 52 weeks the A1c changes were similar and the weight loss was similar  $-4.1$  kg ( $-5.3$  to  $-2.9$  kg) and  $-4.5$  kg ( $-5.7$  to  $-3.3$  kg) in the two groups [67].

The most common side effects of exenatide are predominantly gastrointestinal. Nausea is a common adverse effect, but it is generally mild to moderate in intensity and wanes with duration of therapy [68]. Nausea can be reduced with dose titration. There have been 36 postmarketing reports of acute pancreatitis in patients taking exenatide [69]. In some cases, necrotizing or hemorrhagic pancreatitis was reported, and fatalities occurred. There is insufficient data to determine the overall frequency of pancreatitis in exenatide

users, but overall it seems similar to the background rate in patients with diabetes mellitus.

Liraglutide (Victoza) is another long-acting GLP-1 analog with a 97% structural homology to human GLP-1. It is available for use in the United States, Europe, and Japan for the treatment of type 2 diabetes. The drug is administered subcutaneously once daily. In diabetes trials, liraglutide was associated with a significant reduction in weight (2.0 to 2.5 kg) when compared with placebo or glimepiride [70].

Like exenatide, liraglutide is only available as an injection, in prefilled pens. The initial dose is 0.6 mg once daily for one week to reduce gastrointestinal side effects [71]. After one week, the dose should be increased to 1.2 mg once daily for one week. If blood glucoses remain above the goal range, the dose can be increased to 1.8 mg once daily.

Weight loss has also been studied in patients without diabetes who received liraglutide. In the 20-week study, 564 obese individuals were randomized to one of four liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg) or to placebo administered once a day subcutaneously, or orlistat 120 mg three times a day orally [72]. All individuals had a 500 kcal per day energy-deficit diet and increased their physical activity throughout the trial. Treatment with liraglutide led to a sustained, dose-dependent weight loss that was significantly greater than that with placebo (all doses) and significant for orlistat at the doses of liraglutide of 2.4 mg and 3.0 mg. Mean weight loss with liraglutide ranged from 4.8 to 7.2 kg, depending on the dose. The weight loss was accompanied by reductions in waist circumference, systolic and diastolic blood pressure, and frequency of both metabolic syndrome and prediabetes. Liraglutide was generally well tolerated. However, as in other trials, nausea and vomiting were more frequent with liraglutide than with the other treatments, although these events were mostly of mild or moderate intensity and transient, tending to occur in the first four weeks.

**5.3. Pramlintide.** Pramlintide (Symlin) is an analogue of amylin, a small peptide hormone that is released into the bloodstream by the  $\beta$ -cells of the pancreas along with insulin in response to nutrient stimuli. Amylin has been shown to slow gastric emptying, reduce postprandial rises in blood glucose concentrations, and improve hemoglobin A1C concentrations in both type 1 and type 2 diabetes patients. It must be given by subcutaneous injection, at a maximum dose of 120 micrograms with each meal.

Pramlintide is associated with modest weight loss in patients with type 1 diabetes. In one such trial, where 651 patients with type 1 diabetes were randomly assigned to placebo or subcutaneous pramlintide in addition to their insulin, weight decreased 0.4 kg in the pramlintide group and increased by 0.8 kg in the placebo group [73].

A few trials evaluating the effects of pramlintide on weight in adults with type 2 diabetes have been done. One large double-blind, placebo-controlled trial lasting 52 weeks found that patients treated with pramlintide 30  $\mu$ g, 75  $\mu$ g, and 150  $\mu$ g 3 times daily experienced significant weight loss compared to placebo at weeks 13, 26, and 52. Patients were included in this trial if they were on stable doses of

metformin and/or a sulfonylurea, which is noteworthy since metformin is associated with weight loss and sulfonylureas are associated with weight gain [74]. Another double-blind, placebo-controlled trial confirmed significant weight loss at 52 weeks [75]. In this trial, only the highest dose of 120  $\mu$ g BID treatment group had a sustained weight loss to week 52 ( $P < .05$  versus placebo), whereas in the 90  $\mu$ g BID treatment group, the placebo-corrected treatment difference was no longer significant.

Pramlintide has also been evaluated for the treatment of obesity in adults without diabetes. In two studies in obese subjects pramlintide significantly reduced 24-hr caloric intake by ~500–750 kcal when compared to placebo and also reduced caloric intake by 20% at a highly palatable fast-food challenge [76]. In a 4-month, randomized, double-blind, placebo-controlled, nonforced dose-escalation study in which 88% of subjects escalated to the maximum dose (240  $\mu$ g t.i.d.), pramlintide induced a placebo-corrected reduction in weight of 3.7% ( $P < .001$ ), with 31% of pramlintide-treated subjects achieving  $\geq 5\%$  weight loss (versus 2% for placebo;  $P < .001$ ) [77].

A more comprehensive study assessing the long-term weight loss efficacy and safety of pramlintide at different dosing regimens was carried out in 411 obese subjects [78]. These were randomized to receive pramlintide in one of 7 arms: 120  $\mu$ g b.i.d. and t.i.d., 240  $\mu$ g b.i.d. and t.i.d., and 360  $\mu$ g b.i.d. and t.i.d. or placebo. All subjects received a lifestyle intervention program. At 4 months, 77% opted to continue preexisting treatment during an 8-month single-blind. At month 4, mean weight loss from baseline in the pramlintide arms ranged from 3.8 to 6.1 kg compared with 2.8 kg in the placebo arm. By month 12, the initial weight loss was regained in the placebo group but was maintained in all but the 120- $\mu$ g b.i.d. group. Nausea, the most common adverse event with pramlintide in the 4-month study (9–29% pramlintide versus 2% placebo), was generally mild to moderate and occurred in <10% of subjects during the extension.

## 6. Antiseizure Medications That Lead to Weight Loss

**6.1. Topiramate.** Topiramate (Topamax) is an anticonvulsant agent approved in the mid-1990s for the treatment of refractory seizures in conjunction with other anticonvulsant agents. While it was being studied, it was discovered that the agent mitigated the weight gain often observed with antidepressant treatment. A 6-month dose-ranging study showed that it does so in a dose-dependent manner; the mean percent weight loss was  $-2.6\%$  in placebo-treated subjects versus  $-6.3\%$  in subjects treated with 192 mg/d topiramate for 24 wk [79]. In a meta-analysis of six trials which followed patients for an average of six-months, the weight loss was 6.51% (4.77 to 8.25%) with a placebo effect of about 2.0% [11].

Significant side effects of topiramate included fatigue, paresthesias, difficulty concentrating, 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 [80], markedly lower urinary citrate excretion, and increased urinary pH. These changes increase the propensity of topiramate to form calcium phosphate stones [81]. The high frequency of side effects has led to the termination of phase III trials, while an extended release formulation is being developed by the manufacturer.

**6.2. Zonisamide.** Zonisamide (Zonegran) is another anti-epileptic drug approved by the FDA in 2000 for the treatment of partial seizures in adults with epilepsy. Whereas the anti-convulsant activity of zonisamide is believed to be related to its sodium and calcium channel blocking activity [82], the drug is also known to exert dose-dependent biphasic dopaminergic [83] and serotonergic [84] activity. Weight loss was noted in clinical trials for the treatment of epilepsy [85], hence prompting a trial for obesity.

Only one randomized controlled trial has been done thus far, in which 60 obese subjects on a calorie-restricted diet were randomly assigned to zonisamide (100 mg/d increasing to 400 to 600 mg/d) or placebo for 16 weeks [86]. Mean weight loss in the zonisamide group was 6.6% compared to 1% in the placebo group. In 37 subjects who elected to continue in the trial for an additional 16 weeks, mean weight loss was 9.6 and 1.6% in the zonisamide and placebo groups, respectively ( $P < .001$ ). The most common side effects of zonisamide are cognitive effects and fatigue and a small, but significant, increase in serum creatinine. Zonisamide is not FDA-approved for the treatment of obesity.

## 7. Antidepressant Medications That Lead to Weight Loss

**7.1. Bupropion.** Bupropion is a norepinephrine and dopamine reuptake inhibitor that is approved for treating depression and smoking cessation. Bupropion seems to have a weight-neutral effect for most depressed individuals of normal weight. However, controlled trials with depressed individuals suggest that bupropion SR may be associated with weight loss in overweight or obese subjects [87, 88]. In addition, weight gain after treatment for smoking cessation was less in bupropion SR-treated subjects than in placebo-treated subjects [89].

In a 6-month, randomized, double-blind, placebo-controlled trial 327 obese patients were treated with SR bupropion (300 or 400 mg/d) versus placebo [90]. Initial body percent weight lost for subjects completing 24 weeks was 5.0% for placebo, 7.2% for bupropion SR 300, and 10.1% for bupropion 400 mg/d. Compared with placebo, net weight losses were 2.2% ( $P = .0468$ ) and 5.1% ( $P < .0001$ ) for bupropion SR 300 and 400 mg/d, respectively. Also, there was a 6-month extension where the weight loss was largely maintained. The most common side effects are dry mouth, insomnia, headaches, and nausea. However, other serious adverse events, such as seizures, occur in people who already have a low threshold for seizures. The data is too scant to recommend bupropion as a weight loss drug at this time.

**7.2. Fluoxetine.** Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) approved for the treatment of depression, may also lead to weight loss. A clinical trial of fluoxetine for obesity included a total of 458 subjects who were randomly assigned to fluoxetine (60 mg/d) or placebo. Fluoxetine therapy (60 mg/day) resulted in statistically significantly ( $P \leq .05$ ) greater mean weight loss than placebo at week 28. Although some patients continued to lose weight throughout the 52-week therapy period, maximum mean weight loss occurred at week 20. There was no treatment difference at 52 weeks, meaning that it would not be serving as a long-term medication [91]. In a meta-analysis, trials of fluoxetine as an antiobesity drug at a dose of 60 mg/d, which is three times the usual dose for treatment of depression, produced variable weight change ranging from 14.5 kg lost to 0.40 kg gained [11]. In summary, it can be noted that on average most of the existing medications lead to about a 5% weight loss, with the exception of the sympathomimetic drugs approved for short term use (see Table 1 in supplementary material available online at doi:10.1155/2011/636181).

## 8. New Drugs in Development

**8.1. Leptin.** The protein hormone leptin is produced by adipose tissue and appears to signal adiposity and modulate ingestive behavior [92, 93]. In mice and rare humans with leptin deficiency, administration of physiological doses of leptin decreases food intake and causes weight loss [94]. However, obese adults are found to have high levels of leptin [95], so perhaps there is a state of leptin resistance. If that resistance is overcome with even higher levels of leptin, then perhaps it could lead to weight loss.

A randomized, double-blind, placebo-controlled, multicenter, escalating dose cohort trial was conducted to determine the relationship between increasing doses of exogenous leptin administration and weight loss. In one part of the study 47 obese people on a calorie restricted diet were given either placebo or recombinant leptin at escalating doses 0.01, 0.03, 0.10, or 0.30 mg/kg. By week 24 there was a dose-dependent decrease in body weight, ranging from  $-1.3$  kg in the placebo group to  $-7.1$  kg in the 0.30 mg/kg group ( $P = .01$ ). No clinically significant adverse effects were observed on major organ systems, but it was associated with an unacceptable incidence of injection site reactions [96].

A 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. These metabolic and hormonal changes are reversed to the preweight-reduced state after administrations of low replacement dose leptin. This was seen in a small proof-of-concept study carried out in 10 inpatient subjects where leptin therapy prevented weight gain after significant weight loss, by preventing the weight loss-associated decrease in energy expenditure [97].

**8.2. Peptide YY.** The gut hormone peptide YY (PYY) is synthesized and cosecreted with GLP-1 by the L cells in the

small intestine. It suppresses appetite and decreases food intake [98]. This was illustrated in a trial of obese and lean adults receiving short-term intravenous infusion of PYY administration. Appetite and caloric intake decreased by approximately 30% in both groups when the subjects were offered a buffet meal, and 24 hour caloric intake was reduced. Obese subjects had significantly lower fasting PYY levels and levels correlated inversely with body mass index. These observations suggest that PYY has an important regulatory role in feeding behavior, potentially offering a target for drug development [99].

In contrast, in a 12-week trial, 133 obese patients were randomly assigned to diet and exercise and either intranasal PYY (200 or 600 mcg three times daily before meals) or placebo [100]. The group receiving 600 microg t.i.d. could not be assessed because 59% of the patients discontinued due to nausea and vomiting. There was not statistically significant difference between placebo and the 200 mcg group.

**8.3. Oxyntomodulin.** Oxyntomodulin is a peptide produced in L cells of the GI track from the proglucagon gene product. It is released into the blood in response to food ingestion and in proportion to meal calorie content [101]. Oxyntomodulin has been reported to reduce food intake by 19.3% during an intravenous infusion administered to normal-weight humans, an effect that continues for >12 h after infusion [102].

In a randomized, double blind study oxyntomodulin or saline was self-administered for 4 weeks, three times daily before each meal. The volunteers were asked to maintain their regular diet and level of physical exercise during the study period. Body weight was reduced by  $2.3 \pm 0.4$  kg in the treatment group over the study period compared with  $0.5 \pm 0.5$  kg in the control group ( $P = .0106$ ) [103].

**8.4. Melanocortin-4 Receptor Agonists.** The hypothalamic melanocortin system appears to enhance energy expenditure and suppress appetite. In a study in adults with normal weight, intranasal administration of the MSH/ACTH4–10 core fragment of pro-opiomelanocortin for 6 weeks resulted in a significant reduction of body weight by 1.7 kg [104]. However, a study of 23 overweight men who were given the same compound for 12 weeks did not show any significant decrease in body weight or body fat when compared to placebo [105].

**8.5. Lorcaserin.** Stimulation of specific central serotonin receptors represents an effective pharmacological mechanism to suppress appetite. Serotonin and agonists that activate serotonin 2C (5-HT<sub>2C</sub>) receptors promote feelings of satiety, thereby reducing food intake [106, 107]. Lorcaserin is a selective 5-hydroxytryptamine (serotonin) (5-HT) 2C agonist currently in phase 3 clinical trials for treating obesity. In a 12-week placebo-controlled randomized study of 333 obese individuals taking 10 mg once a day, 15 mg once a day, or 10 mg twice a day, lorcaserin was shown to be associated with dose-dependent weight loss without instructed lifestyle modification; 1.8, 2.6, and 3.6 kg of weight loss, respectively,

were observed over the 12-week period compared with 0.3 kg with placebo [108]. Lorcaserin-treated subjects had reduced plasma cholesterol, waist circumference, fasting glucose, and serum uric acid. Lorcaserin has 7.5-fold selectivity for 5-HT<sub>2C</sub> receptors over 5-HT<sub>2A</sub> receptors and 11.6-fold selectivity for 5-HT<sub>2C</sub> receptors over 5-HT<sub>2B</sub> receptors [109]. In clinical trials, 5-HT<sub>2A</sub> receptor activation, which may cause neuropsychiatric effects, has not appeared to be significantly activated by the dosages used.

**8.6. Tesofensine.** Tesofensine is a sympathomimetic in the family of sibutramine initially developed for the treatment of Parkinson's disease. Although its efficacy was limited for this application, study subjects were noted to experience significant weight loss by appetite suppression [110].

In a recent multidose dose-ranging trial, 203 obese patients were randomly assigned to differing doses of tesofensine (0.25, 0.5, and 1.0 mg) or placebo once daily [111]. After 24 weeks, mean weight reduction was greater in the tesofensine groups (−6.7, −11.3, −12.8 kg, for the three doses, resp.) compared with placebo (−2.2 kg). Common adverse events included dry mouth, nausea, abdominal pain, and diarrhea. Heart rate was significantly elevated in all tesofensine groups (5 to 8 beats per min) ( $P = .0001$ ). The 0.25 dose and the 0.5 mg dose did not show any changes in blood pressure as compared to placebo; however, the highest dose of tesofensine of 1.0 mg daily was associated with a significant increase in systolic and diastolic blood pressure (mean increase 6.8/5.8 mmHg). Insomnia, dry mouth, constipation, diarrhea, and dizziness were also more common. The highest dose of tesofensine showed the highest frequency of mood change. These mild increases in heart rate or blood pressure may end up having clinical significance, as was recently seen in sibutramine.

## 9. Combination Treatments

None of the single-agent drugs that have been approved or appear close to approval has consistently been able to achieve a weight loss of more than approximately 10% of body weight. The combination of phentermine and fenfluramine, which was taken off the market in 1997, was able to achieve a loss of approximately 15% of body weight [112]. Recognizing the complex pathophysiology of obesity, recent efforts have focused on combination therapies. Using more than one drug to treat obesity is similar to treating hypertension, where often several drugs are needed to reach the target goals.

Surprisingly, the combination of orlistat and sibutramine yielded disappointing results. In one trial of 34 obese women who had already lost an average of 11% of their initial weight with sibutramine during the prior one year of treatment, the addition of orlistat to the sibutramine for an additional four months did not induce any further weight loss when compared to sibutramine plus placebo [113]. In a different open-label, randomized, 12-week trial, 86 overweight patients received either orlistat 120 mg three times a day, sibutramine 10 mg/d, the combination of orlistat-sibutramine, or diet [114]. After 12 weeks, sibutramine produced more weight



loss than orlistat alone. The addition of orlistat to sibutramine did not significantly enhance weight loss, similar to the results of the first trial.

A number of novel combination obesity treatments are being investigated in clinical trials. These include phentermine plus topiramate (Qnexa), bupropion plus naltrexone (Contrave), zonisamide plus long-acting bupropion, topiramate and phentermine, and pramlintide plus leptin.

Three phase 3 trials evaluating phentermine plus topiramate (Qnexa) in over 4,500 patients as a treatment for obesity were recently completed under a Special Protocol Assessment by the U.S. FDA. Qnexa is currently under review by the FDA for the treatment of obesity and is not yet approved. EQUATE, the first of the three phase 3 studies, evaluated 756 obese patients over 28 weeks at 32 sites. EQUIP and CONQUER were 56-week studies; EQUIP evaluated 1,267 morbidly obese patients with or without comorbidities, and CONQUER evaluated 2,487 overweight and obese patients with at least two comorbid conditions [115].

The combination of bupropion plus naltrexone (Contrave) is also showing promising effects. Naltrexone, which is used in the treatment of alcoholism, is not associated with weight loss, and bupropion is associated with modest weight loss, but the combination clearly leads to greater effect. The drug was tested in a 56-week clinical trial that enrolled nearly 700 obese people. All study participants enrolled in an intensive weight loss program that included counseling, diet, and exercise. Two-thirds of the study participants also took Contrave. Participants stayed in the program for 56 weeks. By the end, the placebo group, on a weight loss program, lost over 5% of their body weight—11 to 16 pounds, while the Contrave group lost 9.3% of their body weight—20 to 25 pounds. And more than 29% of them lost more than 15% of their body weight. The study had a drop-out rate of over 40%, therefore diluting the effect [115]. On March 31st 2010, Orexigen submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for Contrave. Similar effects were seen with the combination of the long-acting anticonvulsant zonisamide with long-acting bupropion, marketed under Empatic [115].

With the combination of the anticonvulsant topiramate and phentermine in doses one quarter to one-half of those typically used with both agents, weight loss again was seen, with acceptable although definite side effects, including paresthesia in 16–23% versus 3% of those on placebo and dry mouth in 13 and 19% versus none on placebo. An increase in depression and other psychiatric issues were not reported, although there was insomnia in 10–12% versus 6% [116].

In a 24-week study, less than 3% weight loss was seen with pramlintide alone, but 11% weight loss was seen when it was combined with either phentermine or sibutramine. All patients also received lifestyle intervention. Elevations from baseline in heart rate and diastolic blood pressure were demonstrated in both the pramlintide-sibutramine and pramlintide-phentermine group. These results support the potential of pramlintide-containing combination treatments for obesity, but the blood pressure and heart rate changes with sibutramine and phentermine remain a concern [117].

The combinations of pramlintide plus leptin are also being studied. Pramlintide, in a dose 360 micrograms twice daily dose, which is much higher than the 15–120 microgram three times daily usually used in diabetes and metreleptin 5 mg twice daily showed that the agents alone result in a 7% weight loss, but the combination of the two results in a 13% weight loss in completers at 20 weeks [118]. Although the rate of weight loss in the pramlintide-metreleptin arm decreased over time, a plateau was not reached by the end of the study. The most common side effects seen with pramlintide-metreleptin combination treatment were injection site adverse events and nausea, which were mostly mild to moderate and transient in nature.

## 10. Conclusion

Obesity now presents one of the biggest health problems of our times. Diet and exercise are best for both prevention and treatment; unfortunately, both require much discipline and are difficult to maintain. Medications offer a possible adjunct, but their effect is modest, they are limited by side effects, and the weight loss lasts only as long as the drug is being taken, since as soon as treatment is stopped, the weight is regained. Sibutramine, a sympathomimetic medication which was available for long-term treatment, is the most recent of the drugs to be withdrawn from the market due to side effects; in this case it was an increased risk of cardiovascular events. A number of other drugs remain available, but learning more about the combination of existing medications and new drug development will hopefully provide better treatment for this very difficult challenge.

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