

# Advances in Medical Therapy for Weight Loss and the Weight-Centric Management of Type 2 Diabetes Mellitus

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**Abstract** Overweight and obesity are now recognized as leading causes of diseases such as type 2 diabetes, hypertension, hyperlipidemia, and ultimately, cardiovascular disease. Despite the serious consequences, roughly two thirds of Americans are presently classified as overweight, and about one third are classified as obese. Weight loss via lifestyle modification and pharmacotherapy can promote improvement in many of these obesity-related conditions. This review addresses recent advances in pharmacotherapy for the management of obesity and obesity-related co-morbidities, with a focus on the management of obesity specifically in

individuals with type 2 diabetes. Emphasis is also placed on a proposed paradigm shift from the glucose-centric to the weight-centric management of type 2 diabetes mellitus.

**Keywords** Weight loss · Weight management · Obesity · Type 2 diabetes · Pharmacotherapy · Glycemic control · Weight-centric management of type 2 diabetes

## Introduction

The United States is currently facing a very real obesity epidemic. The most recent National Health and Nutrition Examination Survey (NHANES) indicates that approximately two thirds of US adults are presently classified as overweight (body mass index [BMI]  $\geq 25$ ) and one third as obese (BMI  $\geq 30$ ) [1, 2]. Although these numbers alone are formidable, they leave unaddressed the medical costs associated with obesity and obesity-related comorbidities, including type 2 diabetes, hypertension, and dyslipidemia. Recent publications estimated that the annual medical burden of obesity and obesity-related conditions in the United States totaled roughly \$147 billion in 2008 [3], with others projecting obesity-related medical expenses to more than double by 2018, topping \$344 billion, or about 21% of total healthcare spending [4]. Therefore, it is essential to improve our treatment strategies for the management of obesity in order to effectively reduce the rate of obesity-related conditions, not the least of which is type 2 diabetes mellitus.

Weight gain is a side effect of several commonly used diabetes medications. Although medications such as insulin, sulfonureas, and the thiazolidinediones all effectively improve glycemic control and lower HbA1c in patients with type 2 diabetes, they also promote weight gain. Patients can gain as much as 10 kg in a relatively short

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period after initiating these medications [5]. Drug-induced weight gain can have many consequences, including patient noncompliance with treatment regimens once weight gain is noted and health complications associated with the weight gain itself. As was seen in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, tight glucose control without concomitant control of weight does not translate to improved outcomes for diabetics. In ACCORD, extremely tight glucose control in the intensive-therapy group led to higher rates of mortality as compared to the standard-therapy group, which subsequently led to the trial's early discontinuation [6]. What appears noteworthy is that the intensive-therapy subjects also gained weight in the process of having their glucose more tightly controlled, with BMI significantly higher than the conventional-therapy group at the time of study discontinuation, and 28% of the intensive-therapy group gaining greater than 10 kg compared to 14% in the conventional-management group. Although effective control of serum glucose in diabetic patients remains important, it cannot come at the expense of worsening obesity. Even modest weight loss has been shown to significantly improve multiple cardiovascular risk factors, including blood pressure and lipid parameters, while simultaneously improving glycemic control [7]. A paradigm shift is clearly in order, one that promotes weight-centric management of diabetes, rather than a glucose-centric model.

### Indications for Pharmacotherapy and Available Pharmacologic Agents

According to National Institutes of Health (NIH) guidelines, pharmacotherapy for the treatment of obesity can be considered if a patient has a BMI  $\geq 30$ , or has a BMI  $\geq 27$  if weight-related comorbidities, including hypertension, type 2 diabetes mellitus, dyslipidemia, and/or obstructive sleep apnea, are present [8]. With the recent removal of sibutramine from the US market, only orlistat is approved by the US Food and Drug Administration (FDA) for the long-term treatment of obesity. However, there are numerous medications used in the treatment of type 2 diabetes that can promote weight loss, including metformin, GLP-1 analogs, and pramlintide. Medications such as DPP-4 inhibitors and  $\alpha$ -glucosidase inhibitors are considered weight-neutral and therefore are not addressed extensively in this review. The anti-inflammatory salsalate, which has recently been shown to improve glycemic control in patients with type 2 diabetes, appears weight neutral and is also not evaluated [9, 10]. There are, however, investigational medications in the pipeline that may promote weight loss, such as lorcaserin, dapagliflozin, and leptin, that are addressed. Some of the investigational medications being reviewed (phentermine/topiramate and

naltrexone/bupropion) are actually novel combinations of drugs that have already received FDA approval as monotherapies for different indications.

### Orlistat

Orlistat is a gastrointestinal lipase inhibitor that decreases the absorption of dietary fat by 25% to 30% [11], creating a caloric deficit that has been shown to produce statistically significant weight loss. In a 4-year, randomized, double-blind, placebo-controlled study of 3305 obese individuals with and without impaired glucose tolerance [12], subjects lost 5.8 kg with orlistat 120 mg three times daily plus lifestyle modification as compared to 3.0 kg with lifestyle modification plus placebo ( $P < 0.001$ ). After 4 years, the incidence of diabetes in the orlistat group (6.2%) was also found to be significantly lower than in the placebo group (9%;  $P = 0.003$ ). As compared with placebo, subjects in the orlistat group also had significantly decreased waist circumference ( $-6.4$  cm vs  $-4.4$  cm), systolic blood pressure ( $-4.9$  mmHg vs  $-3.4$  mmHg), diastolic blood pressure ( $-2.6$  mmHg vs  $-1.9$  mmHg), total cholesterol levels ( $-7.9\%$  vs  $-2.3\%$ ), and LDL cholesterol levels ( $-12.8\%$  vs  $-5.1\%$ ). Orlistat produces gastrointestinal side effects if too much dietary fat is ingested, often limiting tolerability. A half-dose (60 mg) formulation of orlistat is now available over the counter [13]. Two separate randomized, placebo-controlled trials evaluated the efficacy of thrice-daily orlistat 60 mg versus orlistat 120 mg in combination with lifestyle modification in obese adults over the course of 2 years. After 1 year, mean weight loss was significantly greater in those receiving orlistat 60 mg (7.1–8.5 kg) and orlistat 120 mg (7.9–9.4 kg) than with placebo (4.1–6.4 kg). Roughly two thirds of this weight loss was maintained at the end of the second year in those on orlistat 60 mg (4.5–6.6 kg) and orlistat 120 mg (5.0–7.4 kg), and the losses remained significantly greater than with placebo (1.7–4.3 kg). After 2 years, there were no significant changes in diastolic blood pressure noted in either study, although one of the two studies found that systolic blood pressure was significantly reduced only in the 120-mg orlistat group. Both orlistat groups demonstrated significant improvements in serum lipid levels [14, 15].

### Weight-Centric Management of Type 2 Diabetes Mellitus

#### Lifestyle Plus Metformin

Metformin is an oral anti-hyperglycemic medication approved as first-line therapy in the management of type 2 diabetes. It

has been shown to promote mild weight loss by decreasing hepatic glucose production and intestinal absorption of glucose while improving insulin sensitivity by increasing peripheral glucose uptake and utilization [16]. In combination with lifestyle intervention, metformin has proven to be a potent first step in the management of type 2 diabetes (Table 1). In the Diabetes Prevention Program (DPP), 3234 overweight and pre-diabetic subjects were treated with either lifestyle intervention, metformin 850 mg twice daily, or placebo and followed for an average of 2.8 years. Mean weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively ( $P<0.001$ ). Participants taking metformin 850 mg twice daily reduced their risk of developing diabetes by 31%, with 7.8% of the metformin group subjects developing diabetes each year during the study, compared with 11% in the placebo group. The lifestyle group demonstrated the greatest improvement, with a 58% reduction in the development of diabetes (5% yearly rate). Blood pressure decreased in the lifestyle intervention group but increased in the metformin and placebo groups over time [17]. Additional randomized controlled trials support the finding that metformin as monotherapy has not been found to affect blood pressure in patients with type 2 diabetes [18, 19]. However, metformin has been shown to significantly reduce levels of total and low-density lipoprotein (LDL) cholesterol [20]. Metformin is generally well tolerated but can cause gastrointestinal side effects. Lactic acidosis is a rare but serious complication that can occur due to excess metformin accumulation in the bloodstream, primarily in the setting of significant renal dysfunction [16].

**Table 1** Effect of medications and lifestyle intervention on A1c and weight

Intervention	A1c reduction expected,%	Weight effect
Metformin	1.0–2.0	Loss (0.6–2.7 kg)
GLP-1 analogs	0.5–1.5	Loss (1.8–6.0 kg)
Pramlintide	0.5–0.7	Loss (1.5 kg)
AGIs	0.5–0.8	Neutral
DPP-IV inhibitors	0.5–0.8	Neutral
Sulfonylureas	1.0–2.0	Gain (1.8–5.0 kg)
Meglitinides	0.5–1.5	Gain (0.7–1.8 kg)
TZDs	0.5–1.4	Gain (1.3–4.8 kg)
Insulin	1.5–3.5	Gain (variable)
Intensive lifestyle intervention	0.6	Loss (8.6% of body weight)

A1c glycated hemoglobin; AGIs alpha-glucosidase inhibitors; DPP-IV dipeptidyl peptidase-4; GLP-1 glucagon-like peptide-1; TZDs thiazolidinediones

(From Siram et al. [57]; with permission.)

The Action for Health in Diabetes (Look AHEAD) trial examined the long-term effects of intensive lifestyle intervention (ILI), including decreased caloric intake and increased physical activity, as compared to a control condition involving a program of diabetes support and education (DSE) in 5145 overweight volunteers with type 2 diabetes. According to data from the first 4 years of this trial, ILI participants had a greater percentage of weight loss than DSE participants ( $-6.15\%$  vs  $-0.88\%$ ;  $P<0.001$ ) and greater improvements in HbA1c level ( $-0.36\%$  vs  $-0.09\%$ ;  $P<0.001$ ), systolic ( $-5.33$  vs  $-2.97$  mmHg;  $P<0.001$ ) and diastolic ( $-2.92$  vs  $-2.48$  mmHg;  $P=0.01$ ) blood pressure, levels of high-density lipoprotein (HDL) cholesterol ( $3.67$  vs  $1.97$  mg/dL;  $P<0.001$ ), and triglycerides ( $-25.56$  vs  $-19.75$  mg/dL;  $P<.001$ ) [21•]. Look AHEAD has helped to demonstrate that lifestyle interventions can produce long-term weight loss and sustained beneficial effects on cardiometabolic risk factors.

#### GLP-1 Agonists/DPP-4 Inhibitors

Exenatide and liraglutide are injectable medications indicated for the treatment of type 2 diabetes. They act by mimicking the gastrointestinal incretin hormone glucagon-like peptide-1 (GLP-1), which is normally released in response to food intake. GLP-1 agonists enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion (leading to decreased hepatic glucose output and decreased insulin demand), and slow gastric emptying. Subsequently, GLP-1 agonists have been shown to improve glycemic control, decrease food intake, and enhance satiety. Mild to moderate nausea is the most prevalent side effect noted with the use of GLP-1 agonists [22].

A 24-week, randomized, double-blind, placebo-controlled trial comparing twice-daily exenatide 5  $\mu$ g and 10  $\mu$ g as monotherapy in 232 diabetic subjects demonstrated statistically significant weight loss of 2.8 kg and 3.1 kg for the 5- $\mu$ g and 10- $\mu$ g groups, respectively, as compared to a loss of 1.4 kg for the placebo group. The exenatide groups also demonstrated a placebo-corrected reduction in HbA1c of 0.5% and 0.7% for the 5- $\mu$ g and 10- $\mu$ g groups, respectively, as well as significant, placebo-corrected improvements in mean systolic and diastolic blood pressure for most treatment groups (systolic,  $-3.4$  mmHg for both 5 and 10  $\mu$ g; diastolic,  $-2.0$  mmHg for 10  $\mu$ g) [23].

Three separate 30-week trials were performed to assess the efficacy of twice-daily exenatide 5  $\mu$ g or 10  $\mu$ g versus placebo in combination with either maximally effective doses of metformin [24], sulfonurea [25], or metformin plus sulfonurea [26] in 1446 obese subjects with type 2 diabetes; 314 subjects subsequently completed an optional 52-week open-label exenatide treatment extension. These subjects lost an average of 2.1 kg at week 30, with a total

cumulative weight loss of 4.4 kg after the 52-week extension. At the end of the 52-week extension period, diastolic blood pressure was significantly reduced ( $-2.7$  mmHg) and a trend toward improvement was seen with respect to systolic blood pressure ( $-1.3$  mmHg) [27, 28]. Significant improvements were also noted in mean HbA1c ( $-1.1\%$ ), total cholesterol ( $-2.4$  mg/dL), HDL cholesterol ( $+4.6$  mg/dL), LDL cholesterol ( $-1.6$  mg/dL), and triglycerides ( $-38.6$  mg/dL).

As therapy for type 2 diabetes, Horton et al. [29] compared 6280 subjects receiving exenatide, 5861 subjects receiving sitagliptin, and 32,398 subjects receiving insulin in a retrospective analysis. Sitagliptin is a DPP-4 inhibitor that works by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4), which is responsible for inactivating the incretin hormones GLP-1 and GIP, thus prolonging their activity in circulation [30]. Analysis demonstrated that exenatide-treated subjects lost an average of  $3.0 \pm 7.33$  kg, sitagliptin-treated subjects lost  $1.1 \pm 5.39$  kg, and insulin-treated subjects gained  $0.6 \pm 9.49$  kg. Both systolic and diastolic blood pressure were reduced from baseline to follow-up with all therapies, with reductions of  $2.3 \pm 17.6$  mmHg (systolic) and  $1.2 \pm 10.8$  mmHg (diastolic) for exenatide,  $1.1 \pm 18.2$  mmHg (systolic) and  $0.6 \pm 10.8$  mmHg (diastolic) for sitagliptin, and  $1.8 \pm 21.3$  mmHg (systolic) and  $1.3 \pm 12.5$  mmHg (diastolic) for insulin. Weight loss was significantly associated with reductions in both systolic and diastolic blood pressure in all treatment groups ( $P < 0.0001$  for each).

Liraglutide is a long-acting GLP-1 analogue. Due to its extended half-life [31, 32], liraglutide can be injected as a once-daily therapy. Liraglutide was studied in five separate phase 3 trials entitled Liraglutide Effect and Action in Diabetes (LEAD). The LEAD-3 trial [33•] was a 52-week, double-blind, active-control trial in which two different doses of liraglutide (1.2 mg and 1.8 mg) were compared against glimepiride (a medium to long-acting sulfonurea) in 746 individuals with type 2 diabetes. At 52 weeks, subjects were noted to have a 2.05 kg and a 2.45 kg of weight loss in the 1.2-mg and the 1.8-mg liraglutide groups, respectively, as compared to a 1.12-kg weight gain associated with the glimepiride group. At 52 weeks, liraglutide monotherapy was found to significantly lower HbA1c (0.84% with liraglutide 1.2 mg and 1.14% with liraglutide 1.8 mg) as compared to glimepiride (0.51% decrease in HbA1c). Systolic blood pressure significantly decreased by 2.12 mmHg and 3.64 mmHg in the liraglutide 1.2-mg and 1.8-mg groups, respectively, as compared to a 0.69-mmHg systolic blood pressure decrease in the glimepiride group.

LEAD-2 [34], a 26-week, double-blind, placebo-controlled trial, tested the efficacy of three different doses of liraglutide (0.6, 1.2, and 1.8 mg) when added to metformin as compared with metformin plus glimepiride

and metformin monotherapy plus placebo. The 1091 diabetic subjects had been using metformin monotherapy for greater than 3 months prior to the study's initiation, but remained imperfectly controlled with respect to their diabetes. At the end of 26 weeks, all treatment groups showed significant reductions in HbA1c as compared to the 0.1% HbA1c increase seen in the metformin + placebo group (0.7% reduction for the 0.6-mg liraglutide group, and 1.0% reduction for the 1.2-mg liraglutide group, the 1.8-mg liraglutide group, and the glimepiride group). Weight loss was dose-dependent in the liraglutide treatment groups ( $-1.8$  kg,  $-2.6$  kg, and  $-2.8$  kg for 0.6, 1.2, and 1.8 mg, respectively) and was significantly different from the weight gain seen in the glimepiride group ( $+1.0$  kg). Weight loss in the 1.2-mg and 1.8-mg liraglutide groups was also significantly greater than in the metformin + placebo group ( $-1.5$  kg). In addition, the 1.2-mg and 1.8-mg liraglutide groups had significant reductions in systolic blood pressure of 3.2 mmHg and 2.7 mmHg respectively, compared with an increase of 0.4 mmHg observed in the glimepiride group. The metformin + placebo and liraglutide 0.6-mg groups demonstrated trends toward improvement in systolic blood pressure ( $-1.8$  mmHg and  $-0.6$  mmHg, respectively). There were no significant changes in diastolic blood pressure for any of the groups.

LEAD-5 [35] was a 26-week, double-blind, placebo-controlled trial that examined the effect of liraglutide 1.8 mg when added to metformin plus glimepiride as compared to insulin glargine (a long-acting, peakless basal insulin) when added to metformin plus glimepiride. After 26 weeks of treatment, the HbA1C reduction in the liraglutide group was 1.33%, compared to 1.09% with insulin glargine and 0.24% with placebo. The mean weight loss from baseline of 1.8 kg achieved in the liraglutide group was significantly greater than that in the placebo group ( $-0.42$  kg). Weight increased by 1.6 kg with insulin glargine, resulting in a mean treatment difference of  $-3.43$  kg. A significant reduction in systolic blood pressure was also observed with liraglutide ( $-4.0$  mmHg) as compared with insulin glargine ( $+0.54$  mmHg), but not in comparison to placebo ( $-1.4$  mmHg).

A once-weekly version of exenatide (ExQW) has been submitted to the FDA. DURATION 5 [36], a 24-week comparison versus exenatide twice daily (ExBID), demonstrated that at week 24, ExQW produced significantly greater changes from baseline (least squares mean  $\pm$  SE) versus ExBID in HbA1c ( $-1.6\% \pm 0.1\%$  vs  $-0.9\% \pm 0.1\%$ ;  $P < 0.0001$ ) and fasting plasma glucose ( $-35 \pm 5$  mg/dL vs  $-12 \pm 5$  mg/dL;  $P = 0.0008$ ). Similar reductions in mean body weight from baseline to week 24 were observed in both groups ( $-2.3 \pm 0.4$  kg and  $-1.4 \pm 0.4$  kg). Both treatments were generally well tolerated. Transient and predominantly mild to moderate nausea, the most frequent

adverse event, was less common with ExQW (14%) than with ExBID (35%). Injection-site reactions were infrequent, but more common with ExQW. No major hypoglycemia occurred.

### Pramlintide

Pramlintide mimics the pancreatic hormone amylin, which is normally secreted along with insulin from pancreatic  $\beta$  cells. Pramlintide is approved for use in both type 1 and type 2 diabetes in combination with mealtime insulin, and doses vary for type 1 (30–60  $\mu\text{g}$  subcutaneously before meals) and type 2 diabetes (60–120  $\mu\text{g}$  subcutaneously before meals). As an amylin analog, pramlintide may promote weight loss by slowing gastric emptying, increasing satiety, decreasing postprandial glucagon secretion, and centrally decreasing appetite and total caloric intake. Nausea and headache are the most prevalent side effects noted with the use of pramlintide [36].

Ratner et al. [37] performed a 52-week, randomized, double-blind, placebo-controlled trial in 479 type 1 diabetes patients randomized to placebo, pramlintide 60  $\mu\text{g}$  thrice daily (TID) or 60  $\mu\text{g}$  four times daily (QID) in addition to subjects' normal insulin regimens. At week 52, HbA1c was significantly reduced in both the pramlintide 60- $\mu\text{g}$  TID (−0.29%) and 60- $\mu\text{g}$  QID groups (−0.34%) as compared to placebo (−0.04%). This improvement in glycemic control was associated with weight reduction, which peaked at week 26 in the 60- $\mu\text{g}$  TID (−1.3 kg) and QID (−0.8 kg) groups, compared to a 0.7 kg weight gain in the placebo group. At week 52, mean weight loss for both pramlintide groups was less notable (0.5 kg weight loss) but was still statistically different from the placebo group (0.8 kg weight gain). Subgroup analysis shows that pramlintide prevented weight gain in lean subjects and induced weight loss in overweight and obese subjects compared to placebo-treated subjects, who gained weight during the study. There were no differences in systolic or diastolic blood pressure between the treatment groups [38].

Hollander et al. [39] tested the efficacy of pramlintide in 656 subjects with type 2 DM treated with insulin (alone or in combination with sulfonylureas and/or metformin). During the 52-week trial, subjects were randomized to pramlintide 90  $\mu\text{g}$  twice daily (BID), 120  $\mu\text{g}$  BID, 60  $\mu\text{g}$  TID, or placebo. The 60  $\mu\text{g}$  TID group was excluded from statistical analyses due to limited efficacy. Both remaining pramlintide groups showed significant weight reduction at week 26 compared with placebo (−0.7 kg in the 90- $\mu\text{g}$  BID group and −1.1 kg in the 120- $\mu\text{g}$  BID group compared to +0.3 kg in the placebo group) but at week 52, significance was only sustained in the 120- $\mu\text{g}$  BID group (−1.4 kg vs +0.7 kg in the placebo group). Only the pramlintide 120- $\mu\text{g}$  BID group had significant reductions in HbA1c at both

26 weeks (−0.68%) and 52 weeks (−0.62%). There were no differences in systolic or diastolic blood pressure between the placebo and pramlintide treatment groups.

Aronne et al. [40, 41] assessed high-dose pramlintide monotherapy in 204 noninsulin-treated obese subjects with or without type 2 diabetes. Subjects were randomized to receive either high-dose pramlintide (88% of subjects escalated to 240  $\mu\text{g}$  TID) or placebo before meals for 16 weeks, without lifestyle intervention. Pramlintide produced a placebo-corrected weight loss of  $3.6 \pm 0.6$  kg and a reduction in waist circumference of  $3.6 \pm 1.1$  cm in these obese, noninsulin-treated subjects. Systolic blood pressure decreased by  $3.1 \pm 1.4$  mmHg in the pramlintide group, as compared to a decrease of  $1.4 \pm 1.8$  mmHg in the placebo group. Diastolic blood pressure demonstrated a smaller trend towards improvement, with a  $2.4 \pm 0.8$  mmHg decrease in the pramlintide group, as compared to a decrease of  $1.7 \pm 1.2$  mmHg in the placebo group [40, 41].

Another study aimed at assessing the long-term efficacy of pramlintide monotherapy in conjunction with lifestyle intervention was conducted by Smith et al. [42]. The study consisted of a 4-month, double-blind, placebo-controlled period followed by an optional 8-month single-blind extension period. The nondiabetic, obese subjects were randomized to one of six pramlintide arms (120, 240, 360  $\mu\text{g}$  BID and TID) or placebo. During the initial 4-month period, weight loss from baseline in the pramlintide arms ranged from  $3.8 \pm 0.7$  kg to  $6.1 \pm 0.8$  kg, as compared to  $2.8 \pm 0.8$  kg with placebo (evaluable  $n=270$ ). By month 12, initial 4-month weight loss was regained in the placebo and 120- $\mu\text{g}$  BID pramlintide groups, but was maintained in all other pramlintide groups (12-month evaluable  $n=146$ ). Placebo-corrected weight loss at month 12 for the 120- $\mu\text{g}$  TID pramlintide group averaged  $6.1 \pm 2.1$  kg, with doses higher than 120  $\mu\text{g}$  TID providing little additional benefit. Waist circumference in the pramlintide 120- $\mu\text{g}$  TID group also decreased  $7.9 \pm 1.8$  cm as compared to a decrease of  $4.1 \pm 2.1$  cm in the placebo group. Furthermore, the pramlintide 120- $\mu\text{g}$  TID group demonstrated a  $4.9 \pm 2.1$  mmHg reduction in systolic blood pressure as compared to a  $0.3 \pm 3.2$  mmHg decrease seen in the placebo group, and diastolic blood pressure also demonstrated a trend towards improvement ( $3.0 \pm 1.5$  mmHg decrease) as compared to a  $0.4 \pm 2.8$  mmHg decrease in the placebo group.

### Leptin

Leptin is a cytokine secreted by adipose tissue (in proportion to the body's quantity of adipose tissue) that plays an important role in the regulation of body weight. When secreted, leptin crosses the blood–brain barrier where it binds to its receptor in the hypothalamus. Once bound, leptin activates an intricate array of signals that inhibit food

intake and increase energy expenditure. This complex circuit has yet to be harnessed and fully utilized as an effective treatment modality for the treatment of obesity. Elevated levels of leptin have been found in most obese individuals, leading to the hypothesis that leptin resistance and decreased leptin signaling may be a contributing factor in the obesity epidemic by blunting satiety and energy expenditure signals [41]. Furthermore, when an obese individual begins a hypocaloric diet resulting in weight loss and fat mass is subsequently reduced, a decrease in circulating leptin levels in the face of existing leptin resistance further blunts leptin signaling. As an evolutionary survival strategy, the body thereby defends its body fat by burning fewer calories and decreasing satiety signals. Thus, attempts at weight loss are often thwarted by a relative leptin insufficiency [41].

## Investigational Combination Therapies

### Pramlintide Plus Metreleptin

“The neurohormonal control of body weight involves a complex interplay between long-term adiposity signals (e.g., leptin), and short-term satiation signals (e.g., amylin)... Circulating leptin levels fall rapidly in response to diet-induced weight loss, triggering a host of counter-regulatory metabolic, autonomic, and hormonal responses aimed at defending the initial body weight. Restoration of leptin concentrations to pre-weight-loss concentrations, via administration of metreleptin, has been shown to mitigate weight-loss counter-regulation” [43].

Metreleptin (methionyl recombinant leptin) is an analog of human leptin. Preclinical and clinical evidence recently published in *Proceedings of the National Academy of Sciences of the United States of America* demonstrates that, when pramlintide and metreleptin are administered in combination, leptin responsiveness is at least partially restored by amylin agonism (ie, leptin sensitivity is increased). Experiments in diet-induced obese rats that were co-administered amylin and leptin resulted in synergistic reductions in food intake (up to 45%) and body weight (up to 15%), effects considerably greater than with leptin or amylin treatment alone. Weight loss with amylin/leptin treatment was fat specific and not accompanied by a reduction in lean mass. Translational clinical research confirms that findings in the nonclinical experiments are relevant to human obesity and suggest that metreleptin and pramlintide, when co-administered, may be effective in the treatment of human obesity. The medication was generally well tolerated, with nausea and injection site adverse events observed as the most common side effects [44, 45].

Rasvussin et al. [43] conducted a 24-week (4-week dietary lead-in period, 20-week medication-treatment period), randomized, double-blind, active drug-controlled, proof-of-concept study. The study population consisted of 177 obese or overweight subjects treated for 20 weeks with either a combination of pramlintide 360 µg BID and metreleptin 5 mg BID or matched doses of either medication alone. The data demonstrate that combination therapy led to significantly greater weight loss during the 20-week treatment period ( $-12.7\% \pm 0.9\%$ ) than treatment with pramlintide ( $-8.4\% \pm 0.9\%$ ;  $P < 0.001$ ) or metreleptin ( $-8.2\% \pm 1.3\%$ ;  $P < 0.01$ ) alone. The greater reduction in body weight was significant as early as week 4, and weight loss continued throughout the study without evidence of a plateau [43]. Unfortunately, development of antibodies to native leptin in two of the subjects has stalled this approach.

### Phentermine Plus Topiramate

Low-dose, controlled-release phentermine plus topiramate has been studied as an investigational combination therapy for the treatment of obesity. Topiramate, as monotherapy, is FDA approved as an anti-epileptic and for migraine prophylaxis. Phentermine is an adrenergic agonist FDA approved for the short-term treatment of obesity that is thought to promote weight loss by activation of the central and sympathetic nervous systems, with a subsequent decrease in food intake and increased resting energy expenditure [46].

A meta-analysis [47] evaluated nine randomized controlled trials of phentermine monotherapy for weight loss in obese subjects [48, 49]. The pooled analysis showed that those treated with phentermine along with diet and lifestyle lost 3.6 kg more than those treated with diet and lifestyle alone. Given the increased release of norepinephrine promoted by phentermine, it has the potential to raise blood pressure and heart rate in some patients [48, 49]. A recent study by Hendricks et al. [50] examined the impact of treatment with phentermine monotherapy and a low-carbohydrate diet in 300 obese subjects. Weight loss was significantly greater in the phentermine group as compared to placebo beginning at week 1 and continuing through week 104 ( $P = 0.0144$ ). Additionally, at 52 weeks, systolic and diastolic blood pressure had decreased from baseline in both groups (phentermine: systolic  $-7.3$  mmHg, diastolic  $-5.4$  mmHg; placebo: systolic  $-8.9$  mmHg, diastolic  $-6.3$  mmHg) but the blood pressure difference between groups was not significant despite greater weight loss in the phentermine group. Heart rate changes in the phentermine and placebo groups were also not significantly different at 26 weeks (phentermine  $-0.9$  beats per minute [bpm]; placebo  $-3.5$  bpm) or 52 weeks (phentermine  $+1.2$  bpm; placebo  $-3.6$  bpm) [50].

In the 56-week CONQUER phase 3 trial, 2487 overweight or obese adults with two or more co-morbidities (including hypertension, dyslipidemia, diabetes or pre-diabetes, or abdominal obesity) were randomly assigned to once-daily phentermine 7.5 mg plus topiramate 46.0 mg, once-daily phentermine 15.0 mg plus topiramate 92.0 mg, or placebo. At 56 weeks, change in body weight was  $-1.4$  kg,  $-8.1$  kg, and  $-10.2$  kg in the placebo group, phentermine 7.5 mg plus topiramate 46.0 mg, and phentermine 15.0 mg plus topiramate 92.0 mg groups, respectively. Reductions in systolic blood pressure of  $-4.7$  mmHg and  $-5.6$  mmHg were also seen in the phentermine 7.5 mg plus topiramate 46 mg and phentermine 15 mg plus topiramate 92 mg groups, respectively, as compared to  $-2.4$  mmHg for the placebo group. Less significant reductions in diastolic blood pressure of  $-3.4$  mmHg and  $-3.8$  mmHg were seen in the phentermine 7.5 mg plus topiramate 46 mg and phentermine 15 mg plus topiramate 92 mg groups, respectively, as compared to  $-2.7$  mmHg for the placebo group [51•]. The most significant side effects included dry mouth and paresthesias.

### Naltrexone/Bupropion

A sustained-release (once-daily) combination of naltrexone and bupropion (NB) was recently investigated as a weight loss therapy. Naltrexone is an opioid antagonist FDA approved for the treatment of opioid addiction and alcohol dependence. Bupropion is a norepinephrine and dopamine reuptake inhibitor FDA approved as an antidepressant and to assist in smoking cessation.

NB was studied in a 56-week, randomized, double-blind, placebo-controlled phase 3 trial that included 1742 individuals with either uncomplicated obesity (BMI 30–45) or  $\text{BMI} \geq 27$  to 45 with co-morbidities, including hypertension or dyslipidemia. Participants were prescribed a hypocaloric diet and exercise regimen, and were assigned to receive once-daily naltrexone 32 mg plus bupropion 360 mg, once daily naltrexone 16 mg plus bupropion 360 mg, or placebo for 56 weeks. Mean change in bodyweight was  $-1.3\%$  in the placebo group,  $-6.1\%$  in the naltrexone 32 mg plus bupropion group, and  $-5.0\%$  in the naltrexone 16 mg plus bupropion group. Subjects taking NB also showed significant improvements in risk factors associated with metabolic syndrome including triglycerides, HDL cholesterol, waist circumference, and fasting glucose. A transient increase of approximately 1.5 mmHg in mean systolic and diastolic blood pressure during the first 8 weeks of combination treatment was followed by a return to baseline after week 12, and was subsequently followed by a 1-mmHg decrease below baseline in the naltrexone plus bupropion groups for the remainder of the study. In comparison, the placebo group

demonstrated a 1.5-mmHg reduction in mean systolic and diastolic blood pressure during the first 12 weeks of the study, with further blood pressure reductions afterwards ranging from 1.5 to 3 mmHg below baseline levels. Pulse rate remained stable in the placebo group, and was found to be elevated 1.5 to 2.5 bpm above baseline in the combination treatment groups [52•]. These results prompted an FDA request for cardiovascular outcome studies, which has presently halted NB's progression toward US approval. Additional adverse events include nausea, constipation, vomiting, and dry mouth.

### Investigational Monotherapies

#### Lorcaserin

Lorcaserin is an investigational selective serotonin 2C receptor agonist. The serotonin 2C receptor is expressed in many areas of the brain, including the hypothalamus, an area involved in the control of appetite and metabolism. Agonism of this hypothalamic receptor is thought to promote appetite suppression and increased satiety that may promote significant weight loss.

The phase 3 BLOOM trial [53•] evaluated lorcaserin 10 mg BID as compared to placebo in 3182 overweight and obese adults concomitantly receiving diet and exercise counseling. After 52 weeks, average weight loss was  $5.8 \pm 0.2$  kg in the lorcaserin group and  $2.2 \pm 0.1$  kg in the placebo group ( $P < 0.001$ ). As compared to placebo, waist circumference ( $-6.8 \pm 0.2$  cm vs  $-3.8 \pm 0.2$  cm), total cholesterol ( $-0.9 \pm 0.33$  mg/dL vs  $+0.57 \pm 0.34$  mg/dL), LDL cholesterol ( $+2.87 \pm 0.56$  mg/dL vs  $+4.03 \pm 0.58$  mg/dL), triglyceride levels ( $-6.1\% \pm 1.03\%$  vs  $-0.14\% \pm 0.99\%$ ) HbA1c ( $-0.03\% \pm 0.01\%$  vs  $+0.03\% \pm 0.01\%$ ), heart rate ( $-2.0 \pm 0.3$  vs  $-1.6 \pm 0.4$ ), systolic blood pressure ( $-1.4 \pm 0.3$  vs  $-0.8 \pm 0.3$  mmHg), and diastolic blood pressure ( $-1.1 \pm 0.2$  vs  $-0.6 \pm 0.2$  mmHg) were also significantly decreased in the lorcaserin group. The most common adverse reaction was mild or moderate headache, and no significant increase in cardiac valve abnormalities was noted during the treatment period. Information regarding lorcaserin in combination with other medications is currently unavailable.

#### Dapagliflozin

Dapagliflozin is an investigational medication that inhibits the sodium-glucose co-transporter 2 (SGLT2), and it has been found to improve glycemic control in subjects with type 2 diabetes while also promoting weight loss. SGLT2 is a transport protein located in the kidney that is responsible for glucose reabsorption. Inhibition of SGLT2 by medications such as dapagliflozin promotes urinary excretion of

glucose, thus reducing blood glucose levels when given to diabetics with hyperglycemia and also directly excreting calories in the form of glycosuria [54]. A 24-week, randomized, double-blind, placebo-controlled, phase 3 trial was performed on 546 individuals with type 2 diabetes treated with metformin [55]. After 24 weeks, individuals receiving once-daily dapagliflozin 2.5 mg, 5 mg, and 10 mg plus metformin demonstrated a significant reduction in HbA1c of  $-0.67\%$ ,  $-0.70\%$ , and  $-0.84\%$ , respectively, compared to  $-0.30\%$  for placebo ( $P < 0.0005$  for all treatment arms). Additionally, at 24 weeks, the change in total body weight was  $-2.2$  kg for dapagliflozin 2.5 mg,  $-3.0$  kg for dapagliflozin 5 mg, and  $-2.9$  kg for dapagliflozin 10 mg, compared to  $-0.9$  kg for placebo ( $P < 0.0001$  for all comparisons). Waist circumference decreased in all treatment groups ( $-1.7$  cm,  $-2.7$  cm and  $-2.5$  cm for the dapagliflozin 2.5 mg, 5 mg and 10 mg, respectively) as compared to placebo ( $-1.3$  cm). Significant placebo-corrected reductions in systolic blood pressure (ranging from  $-1.9$  to  $-4.9$  mmHg) and diastolic blood pressure (ranging from  $-1.7$  to  $-2.4$  mmHg) were observed in all treatment groups. Rates of genital infections were higher for the dapagliflozin treatment arms as compared to placebo (8.0–13.1% vs 5.1%), likely from the increased urinary glucose excretion.

A recent meta-analysis [56] of the SGLT2 inhibitors evaluated seven randomized controlled trials ranging from 2 to 48 weeks in duration with variable-dose dapagliflozin and found that average HbA1c was significantly reduced ( $-0.52\%$ ), as was body mass index ( $-1.17\%$ ), systolic blood pressure ( $-4.08$  mmHg), diastolic blood pressure ( $-1.16$  mmHg), and serum uric acid ( $-41.50$   $\mu\text{mol/L}$ ). Dapagliflozin treatment increased the risk of urinary and genital tract infections.

## Conclusions

Although eating too much and exercising too little are clearly involved in the multifactorial genesis of obesity, the propensity to gain weight is inherited and impacted upon by behavioral tendencies, cultural influences, and environmental cues. Many of the medications available for the treatment of diabetes and related conditions may also contribute to obesity. Unfortunately, once weight has been gained, a series of overlapping neuroendocrine responses prevents it from easily diminishing. Furthermore, once weight is effectively lost, a system of counter-regulatory mechanisms increases the hunger response and decreases metabolic rate as a compensatory reaction evolutionarily designed to prevent starvation. Therefore, pharmacologic agents that assist patients in overcoming these neuroendocrine and counter-regulatory responses are necessary in order to produce long-lasting weight loss.

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