Weight Management in Type 2 Diabetes: Current and Emerging Approaches to Treatment

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REVIEW

Diabetes is a growing global health concern, as is obesity. Diabetes and obesity are intrinsically linked: obesity increases the risk of diabetes and also contributes to disease progression and cardiovascular disease. Although the benefits of weight loss in the prevention of diabetes and as a critical component of managing the condition are well established, weight reduction remains challenging for individuals with type 2 diabetes due to a host of metabolic and psychological factors. For many patients, lifestyle intervention is not enough to achieve weight loss, and alternative options, such as pharmacotherapy, need to be considered. However, many traditional glucose-lowering medications may lead to weight gain. This article focuses on the potential of currently available pharmacological strategies and on emerging approaches in development to support the glycemic and weight-loss goals of individuals with type 2 diabetes. Two pharmacotherapy types are considered: those developed primarily for blood glucose control that have a favorable effect on body weight and those developed primarily to induce weight loss that have a favorable effect on blood glucose control. Finally, the potential of combination therapies for the management of obese patients with type 2 diabetes is discussed.

Obesity and diabetes are intimately linked (1). Obesity—in particular abdominal obesity—is a major driver in the development of diabetes and cardiovascular disease (2), with the increasing prevalence of obesity mirrored by the rising prevalence of diabetes (3). In addition, obesity and overweight are associated with multiple comorbidities (4). Weight reduction, therefore, is a key therapeutic goal in both the prevention and management of type 2 diabetes (5).

Weight reduction with intensive lifestyle intervention (ILI) has been shown to reduce the incidence of diabetes by 58% (6). For individuals with diabetes, studies (Look AHEAD [Action for Health in Diabetes], *N* = 5,145) have shown that a loss of 5–10% of body weight can improve fitness, reduce HbA_{1c} levels, improve cardiovascular disease (CVD) risk factors, and decrease use of diabetes, hypertension, and lipid-lowering medications (7,8). Additional benefits of weight loss include reduction of depression symptoms and remission or reduced severity of obstructive sleep apnea (9,10). Greater clinical improvements are observed with greater weight loss (8).

Guidelines recommend lifestyle modifications as the foundation of weight loss. Although ILI produces clinically beneficial weight loss for many patients, the reality is that ILI is difficult to achieve and maintain over the long-term for most patients. Even in an optimal clinical trial setting, such as Look AHEAD, one-third of all patients were unable to achieve at least 5% weight loss after 1 year (11). Most individuals with diabetes tend to lose weight over a period of 4–6 months, and lose 4–10% of their baseline weight before experiencing a plateau in weight loss, generally followed by a

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weight regain (12). In Look AHEAD, half of all patients who lost 5% of their body weight after 1 year of ILI regained some or all of their initial weight loss by year 8 (11). Long-term weight loss is still difficult to achieve for many patients, and alternative options, such as pharmacotherapy, should be considered for patients who cannot lose weight with lifestyle modification alone.

Many conventional glucose-lowering agents commonly result in weight gain (13,14). In addition to antihyperglycemic agents, some antipsychotic medications used to treat comorbid psychiatric disorders and antiepileptic drug derivatives used to treat diabetic neuropathy may lead to weight gain (15,16). Metabolic, psychological, and behavioral factors also affect the ability of people with diabetes to lose weight (17,18). In addition, homeostatic control of body weight is regulated by a complex neurohormonal system that involves a feedback loop between the brain and peripheral tissues, and perturbations to this system affect weight (19). Diet-induced weight loss increases the orexigenic hormones ghrelin and gastric inhibitory/glucose-dependent insulinotropic polypeptide (GIP) and decreases anorexigenic hormones leptin, peptide YY (PYY), cholecystokinin (CCK), amylin, and glucagon-like peptide 1 (GLP-1) (20,21). Improved glycemic control decreases glycosuria, which may impair weight loss. Functional changes within the brain also affect the emotional and cognitive control related to food intake (22). These factors mean that sustained weight loss can be even more difficult to achieve for overweight and obese people with diabetes.

Although improvement of glucose control remains the primary goal in pharmacological treatment of type 2 diabetes, avoidance of pharmacologically induced weight gain should also be considered as a clinically important goal (23). Guidelines recommend lowering HbA_{1c} to ≤6.5% (48 mmol/mol) or ≤7.0% (53 mmol/mol), which often necessitates insulin escalation or use of combination therapies to achieve this goal (5). When considering combination therapies, clinicians should remain aware of the weight gain that is often associated with diabetes medications.

The focus of this review article is to discuss the potential for pharmacotherapies—those currently available and those in either late- or early-stage development—to support the glycemic and weight loss goals of people with diabetes. Although we recognize that bariatric surgery may offer a potential treatment solution for some patients (1), this topic will not be considered in the present review.

WEIGHT GAIN WITH CONVENTIONAL THERAPIES

Many pharmacological agents used in the treatment of diabetes directly contribute to weight gain through their glucose-lowering mechanisms (Table 1) (13,14). The resultant decrease in blood glucose levels corresponds with a decrease in glycosuria, a major contributing factor to the weight gain observed in patients treated with conventional antihyperglycemic agents. Treatment with certain classes of therapies and several baseline patient characteristics are predictive of weight gain (Table 2) (24).

Substantial increases in weight have been observed in patients treated with insulin (24). The mechanisms responsible for insulin-induced weight gain are varied, complex, and partially unknown. Subcutaneous administration bypasses hepatic insulin sensors and leads to physiologically abnormal levels of insulin exposure at peripheral tissues, which may disrupt the homeostatic regulation of body weight (25). A comparative study showed that subcutaneous delivery of insulin leads to more weight gain than intraperitoneal delivery (26). Preclinical research has shown that insulin has a role in the central nervous system, where it regulates satiety signals and suppresses appetite, and it is suggested that these functions may be impaired in type 2 diabetes (27). Insulin-induced hypoglycemia is a further factor; mild hypoglycemia in rats stimulates appetite and leads to the increased consumption of calories (28). Some patients participate in compensatory overeating because of their fear of hypoglycemia (29). Preclinical data indicate that

Table 1—Antidiabetes therapies associated with weight gain

Drug class	Mechanism of action	How mechanism of action leads to weight gain
Insulin* (25,27,28,30,32)	• Regulates glucose metabolism • Lowers blood glucose by facilitating peripheral glucose uptake, primarily by skeletal muscle and fat • Inhibits hepatic glucose production • Inhibits lipolysis • Inhibits proteolysis • Enhances protein synthesis	• Causes hypoglycemia, a potent stimulus to feed • Perceived risk of hypoglycemia may lead to compensatory overeating • Glycemic control reverses the negative energy balance from glycosuria • Insulin is an anabolic hormone and may lead to changes in metabolism that encourage weight gain
Sulfonylurea (24,32)	• Stimulates release of insulin from pancreatic β-cells • May also have mild extrapancreatic effects such as increasing the sensitivity of peripheral tissues to insulin	• Glycemic control reverses the negative energy balance from glycosuria • Causes hypoglycemia, a potent stimulus to feed
TZD (32–35)	• Decreases insulin resistance in the periphery and in the liver • Redistributes fat (less visceral, more subcutaneous)	• Increases adipocyte differentiation • Improves glycemic control • Increases plasma volume

*Most insulins are associated with weight gain; however, insulin detemir has been shown to have a reduced weight-gain effect compared with other insulins (111).

Table 2—Predictors of weight gain*

Baseline patient characteristic predictive of weight gain	Result
Age	• Patients ≤65 years are more likely to gain weight • Patients >65 years are more likely to lose weight
Ethnicity	• Caucasians are more likely to gain weight
Smoking status	• Current smokers are more likely to gain weight
Baseline HbA_{1c}	• Patients with HbA_{1c} >7.2% (55 mmol/mol) are more likely to gain weight • Patients with HbA_{1c} ≤7.2% (55 mmol/mol) are more likely to lose weight

*Based on results from van Dieren et al. (24).

insulin inhibits lipolysis and promotes lipogenesis (30). Generally, insulin has limited effects on resting metabolic rate, and it is unlikely that insulin-induced glucose improvement affects weight through changes in basal energy expenditure (31).

Sulfonylureas are insulin secretagogs that lead to minimal weight gain, compared with insulin, through many of the same mechanisms that occur with insulin use (24). The insulin secretion after sulfonylurea administration lasts for several hours (32), which increases the risk of hypoglycemia and can then cause patients to participate in compensatory overeating. Reduction of glycosuria is another potential mechanism for weight gain with sulfonylureas. Less significant weight-gain effects have been demonstrated with meglitinides—another class of insulin secretagogs—presumably due to their shorter duration of action and associated lower risk of hypoglycemia.

Thiazolidinediones (TZDs) enhance glucose uptake by peripheral tissues through the activation of peroxisome proliferator–activated receptor-γ (PPAR-γ) (33). Activation of PPAR-γ promotes preadipocyte differentiation into smaller, mature adipocytes. Although these smaller adipocytes are more insulin sensitive, PPAR-γ activation triggers an increase in adiponectin secretion from these cells, which may also contribute to the insulin-sensitizing effects of TZDs. Increases in appetite and water retention may also be factors that contribute to TZD-associated weight gain (34). Although TZDs may lead to an increase in fat mass, there is a shift of fat distribution from visceral to subcutaneous adipose depots, which may contribute to the improved hepatic and peripheral tissue sensitivity to insulin observed with TZD treatment (35).

Among traditional glucose-lowering agents, metformin is the only agent that can be considered weight neutral (Table 3) and may even give rise to minimal weight loss (24). The favorable effect on weight observed with metformin use may be due to its ability to reduce energy intake (31).

Table 3—Antidiabetes therapies that are weight neutral or have weight-loss potential

Drug class	Mechanism of action	How mechanism of action leads to weight loss/weight neutrality
α-Glucosidase inhibitors (32)	• Reversibly inhibits membrane-bound intestinal α-glucoside hydrolase enzymes • Delays glucose absorption • Increases GLP-1 secretion	• Weight loss due to inhibition of carbohydrate digestion and delayed gastric emptying via GLP-1
Amylin mimetics (32,68)	• Induces satiety • Slows gastric emptying • Decreases hepatic glucose output by suppressing postprandial secretion of glucagon	• Weight loss due to increased satiety and decreased caloric intake
Biguanides/metformin (31,32)	• Decreases hepatic glucose production • Decreases glucose production • Decreases intestinal absorption of glucose • Improves insulin sensitivity by increasing peripheral glucose uptake and utilization	• May have an anorectic effect
GLP-1R agonists (98)	• Binds and activates the human GLP-1R • Enhances glucose-dependent insulin secretion by the pancreatic β-cell • Increases intracellular cAMP leading to insulin release in the presence of elevated glucose concentrations • Increases satiety	• Weight loss due to inhibition of gastric emptying • Decreased calorie ingestion through central nervous system • Reduced acid secretion
DPP-4 inhibitors (98)	• Increases and prolongs active incretin levels • Increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner	• Slight reduction in caloric intake compensating for reduction in glycosuria
SGLT2 inhibitors (55)	• Binds to SGLT2 receptors and prevents reabsorption of filtered glucose • Lowers renal threshold for glucose • Increases renal glucose excretion	• Calorie loss due to increased renal glucose excretion

ANTIDIABETES THERAPIES WITH WEIGHT-LOSS POTENTIAL

The ability to target poor glycemic control and overweight/obesity simultaneously represents the ideal approach to management of type 2 diabetes (23). Several therapies show promise in this area (Table 3), the most promising of which are considered below.

GLP-1 Receptor Agonists

GLP-1 is an endogenous peptide hormone produced in the gut in response to nutrient absorption. The insulinotropic action of GLP-1 is dependent on glucose (36), which means its activity should not be associated with hypoglycemia. GLP-1 exerts its effects through binding to the GLP-1 receptor (GLP-1R), which is expressed on pancreatic β-cells (37). GLP-1/GLP-1R signaling increases β-cell sensitivity to glucose and suppresses glucagon secretion from pancreatic α-cells (38,39). In addition, GLP-1 exerts extra pancreatic effects, such as reducing hepatic glucose production and inhibiting gastric emptying (39). GLP-1 action at the hypothalamus promotes satiety (40). Because native GLP-1 is rapidly inactivated in vivo, GLP-1R agonists were developed that mimic the actions of GLP-1 in vivo but are resistant to enzymatic degradation and inactivation by dipeptidyl peptidase-4 (DPP-4) (41). GLP-1R agonists exert diverse actions on multiple-target tissues and lead to a reduction in blood glucose and in body weight (42,43).

Exenatide and liraglutide were the first two GLP-1R agonists available for the treatment of type 2 diabetes. In a meta-analysis of randomized controlled trials (RCTs) with exenatide twice-daily and once-weekly (trial durations of 12–52 weeks), the overall reduction in HbA_{1c} from baseline was –1.1% (43). However, clinicians should consider the results from studies of intention-to-treat populations wherever possible, because the weight-loss responses to treatment may differ compared with completer populations (44). The once-weekly extended-release formulation of exenatide has consistently demonstrated weight-loss properties across multiple clinical trials (45,46), showing a mean weight loss of –2.67 kg versus comparator drugs (i.e., exenatide twice-daily, insulin, liraglutide, pioglitazone) (43). Gastrointestinal side effects, such as nausea and vomiting, although rare, occurred as the most commonly reported adverse events (AEs), and most AEs were of mild-to-moderate severity and transient (46). The weight loss observed with exenatide once-weekly was independent of these gastrointestinal AEs. Because exenatide stimulates insulin secretion in a glucose-dependent manner, there was a limited occurrence of major and minor hypoglycemia across clinical trials (46). Liraglutide (1.8 mg q.d.) has similarly been shown to reduce HbA_{1c} (–1.18%) and weight (–3.24 kg) from baseline at 26 weeks (47,48). Liraglutide (1.8 mg q.d.) is generally well tolerated, and the most frequently reported AEs were gastrointestinal (48). In a 26-week study of liraglutide (1.8 mg q.d.) compared with exenatide (10 μg b.i.d.), gastrointestinal AEs resolved more quickly, and fewer cases of minor hypoglycemia were seen in the liraglutide treatment arm (25.5%) than in the exenatide arm (33.6%) (48). Episodes of minor hypoglycemia were thought to be mainly due to the concomitant medications used (sulfonylureas).

Liraglutide (1.2 mg and 1.8 mg) has been investigated in combination with insulin, metformin, sulfonylurea, metformin plus rosiglitazone, or metformin plus glimepiride (49). Significant reductions in HbA_{1c} over baseline were observed within 8 weeks of treatment with liraglutide combination therapy (plus metformin, glimepiride, or metformin plus rosiglitazone; $P < 0.0001$ for all combinations) and were maintained until week 26 (50). The addition of liraglutide to metformin or metformin plus rosiglitazone led to weight reductions, but liraglutide plus sulfonylurea treatment was weight neutral. As with monotherapy, most AEs with liraglutide combination therapy were gastrointestinal in nature (51). Major hypoglycemia was reported only when liraglutide was used in combination with a sulfonylurea. Similarly, exenatide once-weekly has been studied in combination with other antihyperglycemic agents with study durations of 24–30 weeks (52). In combination with metformin, metformin plus sulfonylurea, sulfonylurea with or without TZD, or metformin plus TZD, treatment with exenatide once-weekly led to significant improvements from baseline in HbA_{1c} levels and body weight with all combinations. The most common AEs were hypoglycemia, nausea, diarrhea, and nasopharyngitis; however, hypoglycemia was much lower in patients not on concomitant sulfonylurea therapy.

Although GLP-1R agonists are generally safe and tolerable, postmarketing reports of acute pancreatitis with GLP-1R agonist use have led to pancreatitis being listed under the warnings and precautions in exenatide (twice-daily and once-weekly) and liraglutide U.S. prescribing information (53), and the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), despite a reassuring position statement, continue to investigate this safety signal (54). The current evidence regarding a potential link between pancreatitis and GLP-1R agonist therapies has been conflicting, and large-scale, ongoing, prospective studies will hopefully address questions surrounding a possible association.

Although exenatide and liraglutide are the established GLP-1R agonists in the U.S. and Europe, lixisenatide and albiglutide have been approved in Europe, and albiglutide and dulaglutide in the U.S. Other GLP-1R agonists, such as semaglutide and additional exenatide extended-release formulations (i.e., once-monthly and once-yearly formulations) are under clinical development (53). Clinical trial data show that these therapies provide reductions in HbA_{1c} levels and body weight in people with type 2 diabetes.

Sodium-Glucose Cotransporter 2 Inhibitors

Another new class of antidiabetes therapies that show potential for weight loss (although they are not indicated for weight loss per se) are the sodium-glucose cotransporter 2 (SGLT2) inhibitors (55). In individuals with type 2 diabetes, SGLT2 expression is increased in the renal proximal tubular cells, leading to increased renal glucose reabsorption, which ultimately aggravates hyperglycemia. SGLT2 inhibitors reduce blood glucose mainly through increased glycosuria, although indirect mechanisms have also been reported (23,55).

A meta-analysis of 10 RCTs showed that dapagliflozin (1–50 mg per day) was associated with a reduction in baseline HbA_{1c} of –0.53% in patients with type 2 diabetes (56). In all studies, dapagliflozin monotherapy significantly lowered HbA_{1c}

compared with placebo ($P < 0.01$). Dapagliflozin therapy was associated with a –1.63-kg reduction in body weight and had a favorable weight profile compared with placebo and metformin. Dapagliflozin-induced body weight has been shown to occur through reductions in fat mass, visceral fat, and subcutaneous fat (57,58). Although dapagliflozin monotherapy did not lead to hypoglycemia, the incidence of hypoglycemic events increased when dapagliflozin was combined with sulfonylureas and insulin (56). Dapagliflozin was also associated with an increased risk of mild urinary and genital tract infections compared with placebo.

Multiple studies have demonstrated that canagliflozin (100 and 300 mg q.d.) treatment resulted in significant HbA_{1c} reductions compared with placebo or active comparator (55). After 26 weeks, canagliflozin (100 and 300 mg q.d.) reduced HbA_{1c} levels from baseline by –0.77% and –1.03%, respectively (59). Canagliflozin has demonstrated dose-related reductions in baseline body weight: –2.2% and –3.3% after 26 weeks and –3.3% and –4.4% after 52 weeks for 100 and 300 mg, respectively, in individuals with diabetes (59,60). Canagliflozin (50–300 mg) has also been reported to have beneficial weight effects in overweight or obese individuals without diabetes (61). Overall, the reported incidence of hypoglycemia after 26 weeks with canagliflozin (100 and 300 mg) was low (~3%) and similar to the incidence reported with placebo (59), except in patients on background sulfonylurea (62). The incidence of mild genital mycotic infections and urinary tract infections (UTIs) was higher with canagliflozin treatment than with placebo (59).

In addition to their effect of reducing HbA_{1c} and body weight, dapagliflozin and canagliflozin showed beneficial effects on blood pressure in individuals with type 2 diabetes (55). These effects may be due to increased glucose and sodium excretion in the urine with SGLT2 inhibitors (23). Although increased glucose excretion contributes to the weight loss observed with SGLT2 inhibitor treatment, weight reduction is often limited to <4 kg after even 52 weeks of treatment (55). This attenuation of weight loss may occur because SGLT2 inhibitor–induced glycosuria is accompanied by compensatory hyperphagia, as demonstrated in animal studies (63) and suggested by human studies (64,65).

As with monotherapy, SGLT2 inhibitors combined with other antihyperglycemic agents (i.e., metformin, insulin, sulfonylurea, TZD) have been found to reduce HbA_{1c} (dapagliflozin [1–50 mg]: –0.73%; canagliflozin [50–300 mg]: –0.97%) and body weight (overall: –0.59 kg) (55,66). When used in combination therapy, dapagliflozin and canagliflozin were associated with an increased risk of genital tract infections, whereas dapagliflozin was also associated with a modest increased risk of UTI. However, the number of hypoglycemic episodes experienced by patients treated with SGLT2 inhibitors did not differ from placebo.

Empagliflozin was approved in 2014 by the FDA and EMA to improve glycemic control in adults with type 2 diabetes, and beneficial effects on HbA_{1c} and weight have been observed with empagliflozin as monotherapy or combination therapy (55). A meta-analysis of 10 RCTs found that mean changes in HbA_{1c} were –0.62% for empagliflozin (10 mg) and –0.66% for empagliflozin (25 mg) compared with placebo (67). The incidence of hypoglycemia with empagliflozin treatment was similar to placebo. Mean weight change from baseline was –1.85 and –1.84 kg, with 10- and 25-mg empagliflozin doses, respectively, compared with placebo. Although an increase in the incidence of UTIs was not observed, the risk of genital tract infection was increased with empagliflozin versus placebo.

Additional SGLT2 inhibitors, such as ipragliflozin (approved in Japan) and tofogliflozin, are in clinical development (55). Initial study data have also shown reductions in HbA_{1c} levels and in body weight in people with diabetes.

Pramlintide

Pramlintide acetate is a synthetic analog of human amylin that has been shown to reduce HbA_{1c} and body weight in patients with diabetes (68). It is indicated for the management of type 2 diabetes in the U.S. but is not available in Europe. A meta-analysis showed that in patients with type 2 diabetes, pramlintide is associated with a small but significant reduction in HbA_{1c} (–0.33%, $P = 0.0004$) that is consistent over time (–0.3 to –0.42%; weeks 12–52) (69). Pramlintide was associated with a significant reduction in weight from baseline compared with control (–2.57 kg, $P < 0.00001$), although there was some heterogeneity in the weight-loss data across studies. Pramlintide was associated with a higher incidence of mild-to-moderate, mainly transient, nausea than control. Some studies have reported the incidence of hypoglycemia (mild to moderate) to be higher with pramlintide versus placebo, whereas others have reported the converse (69).

ANTIOBESITY PHARMACOTHERAPIES

Although several antiobesity agents have been withdrawn from the market because of safety concerns, five are now available in the U.S.—orlistat, lorcaserin, phentermine plus topiramate, naltrexone plus bupropion (NB), and liraglutide (3.0 mg) (Table 4) for chronic weight management—and one (orlistat) is currently available in Europe, with liraglutide (3.0 mg) and NB having recently received favorable opinions from the Committee for Medicinal Products for Human Use. These pharmacotherapies have been demonstrated to help people with type 2 diabetes achieve their weight-loss goals and provide them with an HbA_{1c}-reducing benefit (70–73).

Orlistat

Orlistat is indicated for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet, and reduction of the risk of weight regain after prior weight loss (74). Orlistat functions as an antiobesity agent by inhibiting gastrointestinal lipases, thereby reducing absorption of dietary fat (75). In a 4-year study of obese patients without diabetes, orlistat (120 mg t.i.d.) plus lifestyle changes produced moderate weight loss (–5.8 kg from baseline vs. –3.0 kg from baseline with lifestyle changes alone) and resulted in a greater reduction in the incidence of type 2 diabetes over lifestyle changes alone (6.2% vs. 9.0%, a –37.3% reduction; $P = 0.0032$) (76).

Orlistat also provided weight-loss benefits for patients with diabetes. After 52 weeks of orlistat treatment (120 mg t.i.d.) combined with a reduced-calorie diet and a weight-management program, obese patients with type 2 diabetes achieved –5.0% reduction in weight from baseline versus –1.8% with placebo ($P < 0.0001$) and –1.1% HbA_{1c} reduction versus –0.2% with placebo ($P < 0.0001$)

Table 4—Antiobesity therapies currently approved for chronic weight management

Drug	Mechanism of action	How mechanism of action leads to weight loss
Orlistat (75–77)	• Inhibits gastrointestinal and pancreatic lipases	• Prevents absorption of dietary fat
Lorcaserin (71)	• Selectively stimulates 5HT2C	• Promotes feelings of satiety and regulates appetite
Phentermine plus topiramate (80,84)	• Phentermine acts on hypothalamus to stimulate norepinephrine release from adrenal glands • Topiramate acts on multiple cellular targets as an antiepileptic agent	• Promotes feelings of satiety and regulates appetite • The precise mechanisms by which phentermine plus topiramate produce weight loss is unknown
Naltrexone sustained release plus bupropion sustained release (73,86)	• Increases levels of dopamine and POMC neuronal activity • Blocks opioid receptors on POMC neurons, preventing feedback inhibition of these neurons and further increasing POMC activity	• Suppresses appetite • Increases secretion of melanocortins, which mediate anorectic effects and regulate energy balance
Liraglutide (3.0 mg) (98)	• Binds and activates the human GLP-1R • Enhances glucose-dependent insulin secretion by the pancreatic β-cell • Increases intracellular cAMP leading to insulin release in the presence of elevated glucose concentrations • Increases satiety	• Weight loss due to inhibition of gastric emptying • Decreases calorie ingestion through central nervous system • Reduces acid secretion

(70). Retrospective analysis of seven studies of orlistat (120 mg t.i.d.) confirmed that orlistat-treated patients had significantly greater decreases in body weight than the placebo group (–3.77 vs. –1.42 kg, $P < 0.0001$) and larger mean decreases in HbA_{1c} than placebo (–0.74% vs. –0.31%, $P < 0.0001$) (77). For patients with minimal weight loss (<1% of baseline body weight), orlistat still provided a significantly greater decrease in HbA_{1c} than placebo (–0.29% vs. –0.14%, $P = 0.008$). Potential mechanisms to explain the better glycemic control independent of weight loss may be the improvement of insulin sensitivity, slower/incomplete digestion of dietary fat, reduction of postprandial plasma nonesterified fatty acids, decreased visceral adipose tissue, and stimulation of GLP-1 secretion. Orlistat was generally well tolerated, and gastrointestinal effects were the most commonly reported AEs, but all events were considered mild or moderate (75,76).

Lorcaserin

Lorcaserin is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30 kg/m^2 (obese) or ≥27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition such as hypertension, dyslipidemia, or type 2 diabetes (78). In overweight or obese patients without diabetes, lorcaserin treatment provided a −5.81% reduction from baseline body weight after 1 year versus −2.16% with placebo ($P < 0.001$) (79). Lorcaserin is a selective small-molecule agonist of the 5-hydroxytryptamine 2C serotonin receptor (5HT2C), which regulates mechanisms related to satiety, ingestive behavior, glucose tolerance, and hepatic insulin sensitivity (71). Unlike previously available antiobesity agents, lorcaserin has a low affinity for the 5HT2B receptor subtype, whose activation has been linked to the development of valvular heart disease (78).

In a phase 3 study of subjects with type 2 diabetes treated with metformin or a sulfonylurea, lorcaserin treatment resulted in mean weight changes of −4.5% (twice daily) and −5.0% (once daily) compared with −1.5% with placebo at week 52 (71). Participants also showed a significant improvement in glycemic control: HbA_{1c} decreased −0.9% and −1.0% from baseline with lorcaserin twice daily and once daily, respectively, versus −0.4% with placebo ($P < 0.001$ for each lorcaserin dose). It is interesting to note that the reductions in HbA_{1c} observed with lorcaserin are equal to or higher than those observed with other antiobesity agents, such as phentermine plus topiramate and NB, despite a smaller amount of weight loss (71,73,80). This suggests that the antihyperglycemic effect of lorcaserin may be due to more than weight loss alone. Although hypoglycemia was slightly more frequent in the lorcaserin treatment groups than in the placebo group, no severe hypoglycemia was reported (71). No evidence of increased depression, suicidal thoughts, or echocardiogram-detected valvular regurgitations were found in the lorcaserin treatment arms. Overall, the most common AEs with lorcaserin were headache, back pain, nasopharyngitis, and nausea.

Phentermine Plus Topiramate

Phentermine is a norepinephrine- and dopamine-releasing agent (with a lower effect with dopamine vs. norepinephrine) approved for the short-term treatment of obesity (80). Topiramate has several pharmacological mechanisms of action and has been assessed as a single agent for weight reduction in obese patients with and without type 2 diabetes and hypertension (81–83).

A phase 3 study examined the efficacy of the combination of phentermine 7.5 mg/topiramate 46.0 mg (PHEN 7.5/TPM 46.0) or phentermine 15.0 mg/topiramate 92.0 mg (PHEN 15.0/TPM 92.0) on weight loss after 56 weeks (80). Patients

with type 2 diabetes (a subgroup of 388 subjects in this study [*N* = 2,487]) achieved weight reductions of −6.8% with PHEN 7.5/TPM 46.0 and −8.8% with PHEN 15.0/TPM 92.0 versus −1.9% with placebo (80). For patients with diabetes, significantly greater reductions in HbA_{1c} (–0.4 mmol/L) were seen with both doses of PHEN/TPM than with placebo (–0.1 mmol/L). In the 108-week extension study, both doses of PHEN/TPM were associated with significant and sustained weight loss (–9.0%, $P < 0.0001$; placebo, –2.0%) (84). PHEN 7.5/TPM 46.0 and PHEN 15.0/TPM 92.0 led to reductions in HbA_{1c} of –0.4% and –0.2%, respectively, in contrast to the placebo group (0%) (84). Furthermore, in patients without diabetes, the two doses of PHEN/TPM led to 54% and 76% reductions, respectively, in the progression of subjects to type 2 diabetes, compared with placebo (84).

Phentermine plus topiramate was well tolerated; constipation, paresthesia, and dry mouth were the most commonly reported treatment-emergent AEs (84). However, the FDA has required a Risk Evaluation and Mitigation Strategy for phentermine plus topiramate to educate prescribers and patients on the increased risk of orofacial clefts in infants exposed to phentermine plus topiramate during the first trimester of pregnancy (85).

Naltrexone Sustained Release Plus Bupropion Sustained Release

Naltrexone is an opioid receptor antagonist, whereas bupropion is a norepinephrine and dopamine reuptake inhibitor (86). The combination increases proopiomelanocortin (POMC) neuronal firing, which may have anorectic effects. The combination provides greater weight loss than monotherapy with either agent or placebo (86), which is an effect confirmed in overweight/obese patients with type 2 diabetes, hypertension, or hyperlipidemia (23). In patients with type 2 diabetes, NB therapy significantly decreased HbA_{1c} from baseline (–0.6% vs. –0.1% with placebo, $P < 0.001$) (73). NB-treated patients experienced significantly greater weight reduction from baseline than patients in the placebo group (–5.0% vs. –1.8%, $P < 0.001$). Compared with placebo, treatment with NB was associated with a higher incidence of nausea, constipation, and vomiting but was not associated with increased depression, suicidal thoughts, or hypoglycemia. NB may represent a novel pharmacological approach for the treatment of obesity, but further studies are required to assess its effects on cardiovascular outcomes, because systolic blood pressure and pulse rate have been found to be higher with NB than with placebo (78).

Liraglutide

Liraglutide (3.0 mg q.d.) has been shown to provide weight-reduction benefits for obese patients; after 20 weeks, the placebo-subtracted reduction in weight from baseline with liraglutide (3.0 mg) treatment was –4.4 kg (P = 0.003) (87). A further study showed that after 1 year, subjects who received liraglutide (3.0 mg) lost –5.8 kg more than the placebo group, and after 2 years, pooled participants who completed the study on liraglutide (2.4/3.0 mg) maintained a weight loss of –7.8 kg (88). The weight reductions observed with liraglutide (3.0 mg q.d.) primarily result from reductions in fat mass and body fat percentage (including visceral fat) rather than in lean tissue mass (88,89). Similar to liraglutide (1.8 mg) treatment in patients with diabetes, the most common AEs with liraglutide (3.0 mg) treatment in obese patients were gastrointestinal and consistent with the known physiological effects of GLP-1R agonists (88). Liraglutide (3.0 mg) was approved by the FDA in December 2014 for chronic weight management in addition to a reduced-calorie diet and physical activity and is now undergoing EMA regulatory review for the treatment of obesity.

Safety Concerns

Recent safety concerns about an increased risk of major cardiac AEs have led to market withdrawal of existing antiobesity medications or a lack of new treatments being approved (90). Assessment of cardiovascular safety has now emerged as a major consideration for all new antiobesity and glucose-lowering agents under current review by the FDA (91). Given the significant need for effective and safe weight-loss medication, it is perhaps not surprising that many more antiobesity therapies are in development, as detailed in the the recent article by Rodgers et al. (74); these newer therapies are also overviewed below. The potential of these therapies in patients with type 2 diabetes, as well as their cardiovascular safety, will need to be established.

FUTURE PROSPECTS IN CLINICAL DEVELOPMENT

As our knowledge of the physiology of appetite and energy homeostasis improves, so too will our ability to understand how therapies might be combined to provide effective weight management in patients with type 2 diabetes, while also minimizing AEs. Therapies that are currently under clinical investigation are included in Table 5.

GLP-1R Agonists

Similar to liraglutide (3.0 mg), exenatide (10 μg b.i.d.) has been shown to provide weight-reduction benefits in obese people with or without prediabetes (92). After 24 weeks, the placebo-subtracted difference in percentage weight reduction was –3.3% ($P < 0.001$); exenatide-treated subjects lost –5.1 kg from baseline versus –1.6 kg with placebo (92). GLP-1R agonists for oral delivery are also currently under investigation in preclinical and clinical studies (93).

GLP-1R Agonist Combination Therapies

Because GLP-1R agonists and basal insulins offer complementary pharmacologic effects on prandial and fasting glycemia (94), there is growing clinical interest in combinations of these two agents. The combination of exenatide (10 μg b.i.d.) with insulin glargine (approved in the U.S. and Europe) led to greater reductions in HbA_{1c} levels, compared with insulin glargine alone (–1.74% vs. –1.04%). Treatment with exenatide and insulin glargine led to a weight decrease of –1.8 kg, whereas insulin glargine alone led to a weight increase of 1.0 kg. The number of hypoglycemic events between groups did not differ significantly.

Liraglutide with insulin degludec (IDegLira)—now approved in Europe—is another combination currently being investigated for the treatment of type 2 diabetes. Initial clinical data show that IDegLira led to greater reductions in HbA_{1c} (–1.9%) versus insulin degludec (–1.4%) or liraglutide (–1.3%) alone

Table 5—Future prospects

Drug class/combination	Mechanism of action and/or potential for weight loss
Long-acting basal insulin/GLP-1 analog (94,95)	• Acts on receptors for GLP-1 • GLP-1 action suppresses appetite, compensating for a potential insulin-induced weight increase
Pramlintide/metreleptin (100)	• Leptin has a pivotal role in energy metabolism by inhibiting food intake and increasing energy expenditure • Amylin analogs slow gastric emptying
PEG–leptin/GLP-1/glucagon (102)	• Leptin has a pivotal role in energy metabolism by inhibiting food intake and increasing energy expenditure • GLP-1/glucagon coagonism restores leptin responsiveness • Improves glucose and lipid metabolism
Unimolecular dual-incretin agonist (103)	• Acts on receptors for both GLP-1 and GIP • Lowers postprandial glucose through pancreatic β-cell insulin secretion • GLP-1 action suppresses appetite • Increases satiety • Decreases food intake • Decreases fat mass
Unimolecular triple-incretin agonist (104)	• Acts on receptors for GLP-1, GIP, and glucagon • Lowers postprandial glucose through pancreatic β-cell insulin secretion • GLP-1 action suppresses appetite • Decreases food intake • Decreases fat mass • Increases energy expenditure

(95). IDegLira also provided a modest weight loss of –0.5 kg from baseline to week 26, a –2.2-kg reduction, compared with insulin degludec. IDegLira also resulted in significantly fewer hypoglycemic episodes than insulin degludec.

A combination of insulin glargine with lixisenatide has also been investigated (96). The addition of lixisenatide to insulin glargine produced greater reductions in HbA_{1c} (–0.32%; $P < 0.0001$) and postprandial hyperglycemia (difference vs. placebo, –3.2 mmol/L; $P < 0.0001$) compared with insulin glargine alone. The addition of lixisenatide also had a favorable effect on body weight (difference vs. placebo –0.89 kg; $P = 0.0012$). Nausea, vomiting, and symptomatic hypoglycemia were more commonly reported with lixisenatide than with insulin glargine alone.

Another potential future option is a SGLT2 inhibitor/GLP-1R agonist combination (55). The effect of GLP-1R agonists on satiety may weaken the compensatory "overeating" mechanism observed with SGLT2 inhibition and enhance weight loss by SGLT2 inhibitors (63).

FUTURE PROSPECTS IN PRECLINICAL DEVELOPMENT

Given the role of leptin and amylin in controlling food intake and energy expenditure and the role of incretins (GLP-1) in glucose and weight control (97,98), that many of the therapies in preclinical development involve these different hormones is no surprise. Therapies that are currently being studied are included in Table 5.

Peptide Hormone Combination Therapies

Because results with recombinant human leptin or metreleptin (human leptin analog) have been disappointing in reducing HbA_{1c} levels and weight for obese patients with type 2 diabetes (97), approaches are now focused on leptin-related synthetic peptides, such as leptin receptor antagonists or leptin-related synthetic peptide analogs or mimetics, and leptin combination therapies (99). Initial preclinical and clinical data suggest that leptin and amylin—two hormones involved in the control of satiety—have additive effects (99). A proof-of-concept RCT in overweight/obese subjects showed that combination treatment with pramlintide/metreleptin led to a significant earlier, sustained, and greater weight loss than treatment with pramlintide or metreleptin alone (100). However, a subsequent trial was recently halted due to safety concerns (101).

Polyethylene glycolated (PEG)-leptin, along with PEG-GLP-1/glucagon, may be another potential combination therapy option (102). This combination is an intriguing potential antihyperglycemic option, because preclinical data indicate that PEG-leptin and PEG–GLP-1/glucagon coagonism can restore leptin responsiveness, which is often reduced when leptin is used alone. Responsiveness to leptin is associated with decreased food intake, improved glucose tolerance and insulin sensitivity, and with decreased triglycerides and lower plasma cholesterol concentrations. These may be the contributing factors that lead to the weight loss observed with leptin/GLP-1/glucagon coagonism. These results suggest that the pharmacology of leptin in combination with other agents, such as GLP-1R agonists and amylin analogs, warrants additional study as a potential antihyperglycemic therapy that is associated with weight loss.

Another potential therapy is the combination of amylin analogs and GLP-1R agonists. Because both agents can slow gastric emptying, it is possible that these two agents combined may have synergistic effects, but the gastrointestinal tolerance should be evaluated.

Unimolecular Dual- or Triple-Incretin Receptor Agonists

Another incretin pathway compound in early-stage development is a peptide that acts as an agonist at both the GLP-1 and GIP receptors (103). A preclinical study indicates that this dual agonist has the potential to enhance the antihyperglycemic and antiobesity effects observed with monoagonism because it affects adiposity-induced insulin resistance and pancreatic insulin deficiency. A recent study in rodents found that a new monomeric peptide triagonist, simultaneously acting at three key metabolically related peptide hormone receptors (GLP-1, GIP, glucagon), provided additional glucose control and weight-reducing benefits over dual coagonism (104). Extensive clinical investigation into the efficacy and safety of coagonist therapy for the treatment of

patients with obesity and type 2 diabetes is now required.

POTENTIAL THERAPEUTIC TARGETS

Owing to the complex pathophysiology of diabetes, additional therapeutic targets are under investigation as potential agents for glycemic control, many in combination with GLP-1R agonists (105). These possible agents—such as GLP-1R agonist/PYY, fibroblast growth factor 21 with or without GLP-1R agonist, and GLP-1R/glucagon coagonists—may offer the potential to normalize glucose levels but are still in early development (105,106). PYY is an incretin hormone that also has a role in satiety (106). The associated hypothesis is that PYY may further enhance the glucose-lowering and weight-reducing effects of GLP-1R agonists. Fibroblast growth factor 21 has broad metabolic effects, including enhancing insulin sensitivity, decreasing triglyceride concentrations, and inducing weight loss, and this activity acts additively with GLP-1 (107,108). By combining two peptides with different effects, GLP-1R/glucagon coagonism may normalize adiposity and glucose tolerance through fat loss, decreased food intake, and increased energy expenditure, while minimizing hypoglycemic risk (109).

Another agent under clinical investigation as an antiobesity agent is beloranib, a fumagillin-class methionine aminopeptidase-2 inhibitor that has recently completed phase 2 trials (110). Because beloranib treatment is associated with rapid weight loss and improvements in lipids (110), beloranib could likely also have a beneficial effect in the treatment of overweight/obese patients with type 2 diabetes.

Further research with all of these targets is required to determine their suitability as antihyperglycemic agents.

CONCLUSIONS

Although lifestyle interventions aimed at prompting weight loss are important in the management of type 2 diabetes and the benefits of weight reduction are irrefutable, most patients remain overweight or obese. A shift in the approach to weight management in people with type 2 diabetes is clearly needed. Health care practitioners should consider the weight effects of pharmacotherapy in the management of patients with diabetes and consider weight-neutral or weight-reducing medications that can complement the patient's desire for a healthier lifestyle.

For patients struggling to achieve or maintain their weight-management objectives, concomitant antiobesity medications can be considered, with the aim of reducing patients' body weight and glycemic targets. Recent approvals of therapies that provide both glycemic control and weight reduction, and the healthy pipeline of antiobesity medications, bode well for a wider choice in the future, with some agents targeting the central nervous system to reduce food intake and others targeting the hormonal pathways involved in weight regulation and glucose homeostasis. The emergence of a range of pharmacotherapies with varying modes of action, coupled with ongoing improvements in our knowledge of the physiology of appetite and energy homeostasis, provides the prospect of a rational combination therapy that is both effective and tolerable.

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