Obesity Pharmacotherapy in Patients With Type 2 Diabetes

Scott Kahan[1,2] and Ken Fujioka[3]

IN BRIEF Patients with obesity and type 2 diabetes are key targets for weight loss. Given the lack of behavioral weight loss in most patients, obesity pharmacotherapy options should be considered in this patient population. This article reviews key pharmacotherapy options for patients with coexisting obesity and type 2 diabetes. Diabetes medications that are associated with weight gain should be avoided in these patients if possible.

The U.S. Food and Drug Administration (FDA) defines the indication for obesity pharmacotherapy as a BMI >30 kg/m^2 or a BMI >27 kg/m^2 with at least one obesity-associated comorbid condition. Under this definition, nearly 50% of U.S. adults have an indication for obesity pharmacotherapy. Consideration of pharmacotherapy and other treatment escalations beyond or in addition to behavioral counseling is especially important in the subpopulation of patients with obesity and type 2 diabetes given their increased risk of health conditions such as cardiovascular disease and strong evidence of the benefits of moderate weight loss in terms of diabetes control and long-term health. This article focuses on the use of obesity pharmacotherapy in patients with coexisting obesity and type 2 diabetes.

Moderate weight loss yields substantial benefits in patients with obesity and type 2 diabetes. Weight loss of as little as 2–3% from baseline improves glycemic control (reductions in A1C of 0.2–0.3% and in fasting glucose of >20 mg/dL) and triglycerides and decreases the risk for developing diabetes in those at high risk (1). Greater weight loss leads to more significant improvements in glycemic control (a 5% weight loss from baseline improves A1C by 0.5%; a 15% weight loss from baseline improves A1C by ~1.0%) and reduces the need for diabetes medications and yields numerous other health benefits, including reducing blood pressure, improving LDL and HDL cholesterol levels, and improving quality of life (2,3).

Because behavioral treatment alone will lead to sufficient weight loss and health improvements in only a minority of patients, obesity pharmacotherapy is a valuable option for treatment escalation when indicated. Numerous studies have shown the benefit of combining behavioral therapy and pharmacotherapy on weight and glycemic outcomes.

In general, weight loss in patients with diabetes is challenging, and patients with diabetes consistently lose less weight with a given treatment than those who do not have diabetes. This is particularly notable in obesity pharmacotherapy trials, in which weight losses are commonly 25% lower in patients with obesity and diabetes than in patients with obesity but without diabetes.

Why patients with diabetes consistently lose less weight than those without diabetes is not yet fully

[1]*Department of Health Policy, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

[2]*George Washington University School of Medicine, Washington, DC*

[3]*Department of Nutrition and Metabolic Research, Scripps Clinic, La Jolla, CA*

Corresponding author: Scott Kahan, kahan@gwu.edu

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TABLE 1. Diabetes Medications That Tend to Increase Weight, Decrease Weight, or Are Weight Neutral

Medications That Contribute to Weight Gain	Medications That Contribute to Weight Loss	Weight-Neutral Medications
• Sulfonylureas (e.g., glipizide, glyburide, and glimepiride) • Insulins • Thiazolidinediones (e.g., pioglitazone) • Meglitinides (e.g., nataglinide and repaglinide)	• GLP-1 receptor agonists (e.g., exenatide and dulaglutide) • Liraglutide 3.0 mg (a GLP-1 receptor agonist that is also approved for weight loss) • SGLT2 inhibitors (e.g., canagliflozin, dapaglifozin, and empagliflozin) • Others (e.g., metformin and pramlintide)	• DPP-4 inhibitors (e.g., sitagliptin, saxagliptin, linagliptin, and alogliptin) • α-Glucosidase inhibitors (e.g., acarbose and miglitol) • Bile acid sequestrants (e.g., colesevelam)

understood, although there are likely several relevant factors, including genetic, metabolic, and environmental contributors. Notably, as patients with diabetes improve glycemic control, decreased glycosuria, and possibly decreased energy expenditure, occur (4).

Perhaps the most relevant contributor, and one that is readily within the control of health care providers to address, is the use of diabetes medications that are known to contribute to weight gain—especially insulin and sulfonylureas. As diabetes progresses, there is often a vicious circle of increasing β-cell dysfunction and insulin resistance requiring more intensive diabetes medication treatment, which then contributes to further weight gain and worsening of diabetes. In contrast, when diabetes medications with weight loss or weight-neutral properties are used instead of those known to cause weight gain, patients have better glycemic control and lose more weight. The percentage of patients attaining a goal A1C of ≤7.0% is significantly higher in patients receiving diabetes medications that are weight neutral or have weight loss side effects (5). Table 1 lists several diabetes medications and their tendency to increase, decrease, or have no effect on body weight. Of note, although there are several diabetes medications that contribute to weight loss, only liraglutide—at a higher dose than that approved for diabetes (3.0 mg)—achieves sufficient weight loss outcomes to be formally approved for obesity treatment.

TABLE 2. Common Medications for Weight Loss in Patients With Diabetes

FDA-Approved Medications for Weight Loss	Medications Not Explicitly Approved for Weight Loss
• Liraglutide 3.0 mg	• Metformin
• Naltrexone-bupropion SR	• Pramlintide
• Lorcaserin	• SGLT2 inhibitors
• Phentermine	• SGLT2 inhibitors + phentermine
• Phentermine-topiramate ER	
• Orlistat	

ER, extended release; SR, sustained release.

Obesity Pharmacotherapy Options for Patients With Diabetes

Several medications have been approved for the treatment of obesity, all of which lead to clinically meaningful weight loss of ~5–15% of baseline weight and A1C reductions of 0.5–1.6% in patients completing at least 1 year of medication treatment (Table 2). Obesity pharmacotherapy can also counter the weight gain associated with diabetes medications that tend to cause weight gain. Weight loss and glycemic control are significantly improved when pharmacotherapy is combined with behavioral therapy. Behavioral counseling, discussed elsewhere in this issue (p. 237), generally precedes pharmacotherapy, although recent guidelines suggest consideration of primary pharmacotherapy in patients with obesity and either diabetes or prediabetes, even if counseling alone has not previously occurred, because of the high risk in this patient population (6).

Liraglutide 3.0 mg

Liraglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist that was approved in 2010 under the brand name Victoza (liraglutide 1.8 mg) for the treatment of type 2 diabetes. It has since been studied and approved by the FDA in 2015 for the treatment of obesity, under the brand name Saxenda, albeit at the higher dose of 3.0 mg daily. Liraglutide is the only diabetes medication to be explicitly approved for weight management. The medication is administered subcutaneously via a pen injection device.

Liraglutide, like other GLP-1 receptor agonists, has a number of mechanisms of action, including stimulation of insulin secretion, improved insulin sensitivity, suppression of glucagon, and decreased gastric emptying. However, the

mechanism of action that is believed to be most relevant with respect to weight loss is a centrally acting, satiety-inducing effect on neurons in the arcuate nucleus of the hypothalamus. When humans consume food, numerous hormones, including GLP-1 are released from the small intestine and feed back to the hypothalamus to signal satiety, essentially signaling that food has been consumed and the relentless drive for food seeking can be temporarily turned off (7–9).

Liraglutide administration leads to a dose-dependent weight loss response. In a 20-week (phase 2) clinical trial, liraglutide 1.8 mg led to a 5.5-kg weight loss, which plateaued by 20 weeks, whereas liraglutide 3.0 mg led to a 7.2-kg weight loss, which continued to trend toward further weight loss as the short trial ended (10). Phase 3 trials with 1-year duration confirmed this, showing that weight loss with liraglutide 3.0 mg continued through at least 1 year, with average weight loss at 56 weeks approaching 10 kg (11).

In patients with diabetes and obesity, liraglutide 3.0 mg leads to impressive improvements in weight and diabetes control. In the SCALE Diabetes trial, which randomized 846 patients with diabetes to either liraglutide or placebo, those assigned to liraglutide 3.0 mg lost 6.0% of their baseline body weight, compared to 4.7 and 2.0% weight losses in patients randomized to liraglutide 1.8 mg or placebo, respectively (12). Approximately three times as many patients taking liraglutide 3.0 mg lost at least 5 and 10% of their baseline body weight compared to those assigned to placebo. Those randomized to liraglutide 3.0 mg had an A1C improvement of 1.3%, compared to improvements of 1.1 and 0.3% with liraglutide 1.8 mg and placebo, respectively.

There are two key prescribing recommendations that improve tolerability and outcomes: slow titration and attention to responsiveness.

Liraglutide should be prescribed at an initial dose of 0.6 mg daily during the first week of treatment and gradually titrated up by 0.6 mg weekly until the dose of 3.0 mg is achieved, which usually occurs by the fifth week of treatment. This slow titration minimizes the likelihood of side effects, especially nausea and gastrointestinal (GI) disturbances. Nausea is the most common side effect of liraglutide. When it occurs, it tends to increase during the first few weeks of titration and generally diminishes over the course of several weeks to months. In the authors' experience, when nausea or other side effects are limiting, this titration can be further slowed for as long as necessary, and, in some cases, lower doses can be used indefinitely, as long as patients are experiencing benefit.

A second recommendation is to evaluate patients' responsiveness to treatment. The FDA recommends evaluating weight loss after 16 weeks of treatment. Patients who lose ≥4% of their baseline weight during this time will likely continue to lose weight, whereas those who lose <4% of baseline weight are unlikely to lose significantly more weight with continued treatment. Thus, it is advised to stop medication for those in the latter group.

During the pivotal trials, 77.2% of patients were responders (≥4% weight loss during the initial 16 weeks), and this group lost 10.8% of their baseline body weight at the end of 1 year of treatment, compared with just 3% weight loss for nonresponders. In patients with diabetes being treated with liraglutide 3.0 mg, responders lost 8.5% of their weight at the end of 1 year, compared to a 3.1% weight loss in nonresponders (13). A 3-year study following responders who initially had prediabetes showed the weight loss experienced at 1 year was mostly maintained through 3 years of treatment, and progression to diabetes was reduced by nearly 80% compared with those who received placebo (14). It is not yet known what distinguishes responders from nonresponders, although genetic underpinnings are believed to be important, and it is anticipated that future pharmacogenetic research will lead to opportunities to identify likely responders before starting treatment.

Overall, the most common side effects of liraglutide 3.0 mg are GI-related, and especially nausea. Risks exist for thyroid C-cell tumors (in rodents) and acute pancreatitis; both are known risks of the broad GLP-1 receptor agonist class of medications. This medication should be avoided in patients with history of medullary thyroid carcinoma or pancreatitis. The most notable risk in patients with diabetes is hypoglycemia. Asymptomatic hypoglycemic is common in patients with and without diabetes, although symptomatic hypoglycemia is far more common in patients with diabetes, and severe hypoglycemia has only been reported in patients taking concomitant sulfonylurea medications (15).

Naltrexone-Bupropion Sustained-Release

Naltrexone-bupropion sustained-release (SR), which is FDA-approved under the brand name Contrave, is a combination of naltrexone and bupropion in a sustained-release formulation that works in multiple ways to decrease food intake and weight. Bupropion is a norepinephrine and dopamine reuptake inhibitor, and naltrexone is an opioid receptor antagonist. Animal studies suggest that, when used together, bupropion and naltrexone increase the firing rate of pro-opiomelancortin neurons in the hypothalamus, in part as a result of naltrexone-induced reduction in an autoinhibitory effect of β-endorphins, leading to diminished appetite and food intake (16). Additionally, this combination medication also affects reward-driven eating and decreases cravings for high-calorie, pleasurable foods (17,18). This effect occurs as a result of action in the mesolimbic system of the brain, which controls

reward-driven behavior to pleasurable activities and is responsible for cravings for highly palatable foods in response to various food cues (19). Of note, this medication may have particular benefits in patients with depression or tobacco use because bupropion has been approved for both indications; of note, however, the combination of naltrexone and bupropion has not been explicitly approved for these purposes.

Several phase 3 randomized, controlled clinical trials have been completed showing impressive weight loss and improvement in obesity-related comorbid conditions. In a trial of naltrexone-bupropion SR in patients with obesity and type 2 diabetes, those who were treated with the medication for 1 year lost 5.9% of initial body weight and had an A1C reduction of 0.6% compared to a 2.2% weight loss and 0.1% A1C reduction in the placebo group (20).

As described above with respect to liraglutide, there are two key prescribing recommendations that improve tolerability and outcomes.

The most common adverse events (AEs) in the clinical trials were nausea and vomiting, which occur in 30–40 and 15–20% of individuals, respectively, depending on the population studied (21). Slow titration is recommended, whereby the dose is slowly increased from 1 tab (8 mg naltrexone/90 mg bupropion) daily to the therapeutic dose of two tabs twice daily (32 mg naltrexone/360 mg bupropion) over the course of 4 weeks. This phased titration greatly improves tolerability, especially with respect to nausea and vomiting, although some patients may benefit from even slower titration. Although the weekly escalation schedule was "forced" in the clinical trials (i.e., doses had to increase according to this schedule regardless of whether the medication was well tolerated), to further improve tolerability in clinical practice, we recommend for patients who continue to experience side effects an even slower titration schedule, which may take several months to achieve the therapeutic dose (22).

As with liraglutide, it has been shown that early weight loss predicts long-term success with this medication. In a pooled analysis of phase 3 trials, weight loss of ≥5% at 16 weeks of treatment predicted average weight loss of 11.7% at the end of 1 year (23). Thus, it is recommended that patients who achieve ≥5% weight loss by week 16 continue the medication, whereas those who do not achieve this threshold should consider discontinuation because they may not be getting sufficient benefit.

This medication is contraindicated in patients with uncontrolled hypertension, those being treated with chronic opioid medications or monoamine oxidase inhibitor medications, and those at high risk for seizures. There is a warning that young adults and adolescents may experience suicidal thoughts when treated with bupropion. Finally, asymptomatic hypoglycemia is common, although symptomatic or severe hypoglycemia has been found to occur only in patients with diabetes taking concomitant medications such as sulfonylureas that increase the risk of hypoglycemia.

Lorcaserin

Lorcaserin is a selective serotonin-2c (5HT-2c) receptor agonist, which specifically stimulates the 5HT-2c receptors in the hypothalamus, leading to increased satiety and weight loss. As opposed to earlier serotonin agonists that were used off label for weight loss, lorcaserin primarily stimulates the 2c subtype rather than other serotonin receptors in the brain and body, thereby leading to fewer AEs and risks of treatment (24). Lorcaserin was approved by the FDA in 2012 under the brand name Belviq, initially at a dose of 10 mg twice daily, and has since also been approved as Belviq XR (20 mg).

Treatment with lorcaserin leads to a 7–8% body weight loss, on average, in patients completing 1 year of treatment (25). Patients with type 2 diabetes treated with lorcaserin lost 4.5–5% of baseline body weight, depending on the dose administered, and achieved an improvement in A1C of 0.9–1.0% compared to 1.5% weight loss and 0.4% A1C improvement in those taking placebo (26,27). In one study, patients with prediabetes and obesity who were treated with lorcaserin had a 38% lower risk of developing type 2 diabetes than patients treated with placebo (28).

Patients who respond to lorcaserin usually do so relatively quickly. Therefore, response to treatment should be evaluated 12 weeks after initiation. If patients lose ≥5% of their weight from baseline, they will likely continue losing weight, with weight loss at the end of 1 year exceeding 10%, so the medication should generally be continued. For patients who do not lose ≥5% of initial body weight after 12 weeks, the medication is generally discontinued because there is a low likelihood of further weight loss (29).

Lorcaserin is classified as a schedule IV substance. Dosing is 10 mg twice daily or 20 mg XR once daily and does not require titration. The most common AEs are headache, dizziness, fatigue, nausea, dry mouth, and constipation, although these are relatively uncommon and rarely lead to treatment discontinuation. In some patients, hypoglycemia may occur when lorcaserin is taken concomitantly with blood glucose–lowering agents for diabetes, and it is recommended that medications such as sulfonylureas be discontinued or doses lowered when starting treatment with lorcaserin. As with all obesity medications, lorcaserin is contraindicated during pregnancy and lactation. Caution is necessary if patients are being treated with serotonergic or antidopaminergic medications, which can, rarely, precipitate serotonin syndrome or neuroleptic malignant syndrome. Other warnings include caution in

patients with valvular heart disease, congestive heart failure, or psychiatric disorders and those at risk for priapism (30).

Phentermine-Topiramate Extended-Release

The combination of phentermine and topiramate, approved by the FDA in 2012 and sold as Qsymia, takes advantage of the additive weight loss effects of these medications. Phentermine, a sympathomimetic amine, has been approved for short-term weight loss since 1959; by itself, it decreases appetite and leads to moderate weight loss. Topiramate, which has multiple mechanisms of action, is approved as monotherapy for migraine and seizure prevention. On average, topiramate alone leads to relatively little weight loss. However, together, these medications lead to impressive weight loss at quite low doses.

In the SEQUEL trial (31), a 2-year evaluation of phentermine-topiramate extended-release (ER) versus placebo, patients treated with the medication lost ~10% of their body weight on average, compared to <2% in the placebo group. In the EQUIP trial (32), patients with severe obesity (BMI ≥35 kg/m^2) who completed 1 year of treatment with phentermine-topiramate ER 15/92 mg lost 14.4% of body weight compared with 2.1% in the placebo group; 83.5% lost at least 5% of body weight, compared with 25.5% in the placebo group, and 67.7% lost at least 10% of body weight compared with 13.0% of those completing placebo treatment. Sub-analysis in patients with extreme obesity (BMI >45 kg/m^2), a population rarely studied for nonsurgical weight loss interventions, showed that >50% of patients who completed the trial lost >15% of their initial body weight, and 28% of patients lost >20% of their initial body weight (33).

Patients with type 2 diabetes in the SEQUEL trial maintained a 9% weight loss over 2 years, compared to a 2% weight loss in the placebo group (31). Patients treated with the medication also had improved cardiometabolic markers, including reduced blood pressure and lipids, and many were able to decrease or discontinue blood pressure and diabetes medications. In patients with prediabetes, progression to type 2 diabetes was reduced by 76% compared to placebo in patients treated with the higher dose (15/92 mg) of the medication. In a clinical trial of 130 patients with type 2 diabetes, those randomized to phentermine-topiramate ER lost 9.4% of baseline weight, compared to 2.7% weight loss in those assigned to placebo. A1C was reduced by 1.6% in the treatment group, compared to 1.2% in the placebo group (34).

Treatment is initiated at 3.75 mg phentermine/23 mg topiramate ER and escalated to 7.5/46 mg after 2 weeks. Patients' response should be evaluated after 12 weeks at this dose; those who achieve a weight loss ≥3% should continue the medication, whereas those not achieving this degree of weight loss should increase their dose (to 11.25/69 mg, followed by 15/92 mg) or discontinue the medication. The most common AEs are paresthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth, which are usually mild and transient. Approximately 3% of patients on the lower doses and 9% on the highest dose discontinue the medication due to an AE (35).

Phentermine-topiramate ER is classified as a schedule IV controlled substance. It is contraindicated during pregnancy and lactation. However, because topiramate is a known teratogen (that can cause cleft lip/palate), pregnancy should be ruled out before starting the medication, and women of childbearing age should be advised to use contraception and to have monthly pregnancy testing during use. It is notable, however, that a large study of >800,000 subjects did not find an increased risk of birth defects (36). Other contraindications include glaucoma, use of monoamine oxidase inhibitor medications, and hyperthyroidism. If discontinuation is necessary, patients treated with the highest dose (15/92 mg) require tapering by taking the dose every other day for 1 week before discontinuing; patients taking other doses can discontinue the medication without weaning (35).

Orlistat

Orlistat is the only noncentrally acting medication for obesity treatment. It is a pancreatic lipase inhibitor that decreases absorption of ingested fat. The medication is dosed thrice daily with meals. It was initially approved by the FDA in 1999 as Xenical and has since been approved for over-the-counter use at half-dose (60 mg), branded as Alli.

Several studies have shown that orlistat leads to moderate weight loss. Most notably, the XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) trial showed that orlistat plus behavioral counseling led to meaningful weight loss through 4 years of therapy, yielding approximately twice the weight loss of counseling plus placebo. Among 3,305 patients randomized to orlistat or placebo, those in the orlistat group lost 10.6 kg at 1 year and maintained a loss of 5.8 kg at 4 years, compared to 6.2 and 3.0 kg, respectively, at 1 and 4 years in the placebo group. Among patients with impaired glucose tolerance at baseline, the risk of progression to type 2 diabetes was reduced by 45% compared to the placebo group (37). In patients with type 2 diabetes, orlistat reduces A1C by ~0.3–0.5% when used in combination with oral antidiabetes medications or insulin (38–40).

Patients using orlistat should be counseled on the risk of GI AEs such as diarrhea, flatulence, or other GI complaints, when consuming large amounts of fat while taking the medication. Although these and other GI AEs are common, it is notable that, in the XENDOS trial, far more patients in the orlistat group than in the placebo group completed the trial

(52 vs. 34%), suggesting that the side effects are reasonably tolerated when the medication is taken as prescribed. Because orlistat binds to fat-soluble vitamins, patients are at risk for deficiencies. Thus, they should be advised about the need for a nutritionally balanced, reduced-fat, and reduced-calorie diet, and they should take a multivitamin that contains fat-soluble vitamins separately from the medication (at bedtime). Orlistat should not be used in patients with cholestasis or chronic malabsorption syndromes. Further warnings include coadministration with cyclosporine, which leads to a decrease in the absorption of cyclosporine and an increased level of urinary oxalate, which may predispose patients to kidney stones (41).

Additional Pharmacotherapy Considerations

The medications described above are FDA-approved for obesity treatment and have been studied explicitly in patients with type 2 diabetes. We briefly describe below several additional options that may be considered for weight loss in patients with diabetes but have either not been formally approved for this purpose or do not have sufficient data in patients with type 2 diabetes. We also briefly mention several medications in the pipeline that may soon be evaluated for obesity pharmacotherapy approval by FDA.

Metformin

Metformin has a long history of use in patients with diabetes and prediabetes and was one of the first antidiabetes medications that did not increase the risk for weight gain. It is widely considered a first-line medication for type 2 diabetes and for diabetes prevention (42). Metformin has several mechanisms of action that are believed to be related to weight loss, including stimulating pro-opiomelanocortinin neurons in the hypothalamus, improving leptin and insulin sensitivity, increasing GLP-1 levels, and modulating gut flora (43). Numerous studies show that metformin leads to decreased food intake of ~250–300 kcal per day and moderate weight loss in the range of 2–4 kg (26,44–46).

Pramlintide

Amylin is a pancreatic hormone that is co-secreted by β-cells in a one-to-one ratio with insulin in response to a meal. Amylin has been shown to slow gastric emptying, suppress glucagon secretion, and lower food intake. Importantly, amylin increases energy disposal by preventing compensatory decreases of energy expenditure in weight-reduced individuals (47). Pramlintide is an analog of human amylin that is approved for patients with type 1 or type 2 diabetes who have not achieved desired glucose control despite the use of mealtime insulin. In human studies, pramlintide, acting as an amylin analog, slowed gastric emptying, reduced the postprandial rise in glucagon, and increased satiety leading to decreased caloric intake (48). Among patients with obesity but without diabetes, a 16-week trial showed improved appetite control and weight loss 3.7% greater than with placebo. A 12-month trial found weight loss of 6.3–8.0 kg with higher doses of pramlintide (49,50).

In a meta-analysis of four clinical trials with 930 patients with type 2 diabetes who were being treated with insulin, pramlintide treatment led to a mean weight loss of 2.6 kg and A1C reduction of 0.3–0.4% compared to placebo (51).

Combination therapy with pramlintide and recombinant leptin has been proposed and studied as a novel obesity treatment. In one study, patients were started on pramlintide to obtain a target weight loss of 2–8%, and then recombinant leptin was added. Patients who completed treatment with pramlintide and leptin had a mean weight loss of 12.7% from baseline and were still losing weight at the completion of the study. Unfortunately, a confirmatory clinical trial (clinicaltrials.gov identifier NCT01235741) was discontinued before completion of enrollment because of the identification of potentially neutralizing anti-drug antibodies to leptin in previously exposed patients (52).

As with many GI hormones that slow gastric emptying and have known receptors in the brain, nausea is a common side effect of pramlintide, affecting 28–48% of patients. Slower and longer titration after treatment initiation may minimize nausea and improve tolerability, and many patients may not tolerate the full dose but still experience a beneficial response at lower doses.

Semaglutide

Semaglutide is a human GLP-1 analogue with a similar structure to liraglutide that is currently in development for the treatment of type 2 diabetes and obesity and not yet approved by the FDA. In a 12-week trial in which patients with obesity received a 1-mg once-weekly subcutaneous dose of semaglutide, weight decreased by 5 kg, energy from ad libitum meals was reduced by 24%, and patients experienced less hunger and cravings, better control of eating, and a lower preference for high-fat, energy-dense foods (53). In patients with diabetes randomized to either semaglutide or insulin, weight decreased 5.2 kg with semaglutide compared to weight gain with insulin. A1C decreased 1.6%, which was twice the A1C reduction of patients treated with insulin (54). Moreover, a cardiovascular outcomes trial in high-risk patients with type 2 diabetes showed impressive weight loss, improvements in glycemic control, and significantly lower rates of cardiovascular death and nonfatal myocardial infarction and stroke in patients treated with semaglutide compared to placebo (55).

Combined Phentermine and Sodium–Glucose Cotransporter 2 Inhibitor

Phentermine, as described above, has been used for decades for short-term weight loss treatment. Aside

from two very small studies conducted in the 1970s, phentermine as monotherapy has not been explicitly studied in patients with type 2 diabetes (56,57). Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a newer class of medications approved for type 2 diabetes that act by blocking the SGLT2-induced reabsorption of glucose in the proximal tubules of the kidneys, thereby causing glycosuria, weight loss, and improved glycemic control. The degree of glucose-calorie excretion induced by SGLT2 inhibitor therapy—~90 g glucose/day or 360 calories/day—significantly exceeds the observed weight loss associated with this medication. It has been hypothesized that SGLT2 inhibitor therapy causes a compensatory increase in appetite and food intake, minimizing weight loss outcomes. A 26-week randomized trial in patients with obesity but without type 2 diabetes showed that treatment with a combination of canagliflozin and phentermine led to a 6.9% greater weight loss than placebo (27). This combination option is being further studied in hopes of future approval for obesity treatment.

Conclusion

Given the high prevalence of type 2 diabetes and its strong association with excess weight, use of obesity pharmacotherapy should be considered in appropriate patients with diabetes and excess weight. Glycemic control begins to improve with as little as 2–3% weight loss, and there is generally a linearly increasing glycemic improvement with further weight loss. Medications should be chosen based on clinical indications, degree of weight loss and glycemic improvement targeted, and individual patient considerations.

Duality of Interest

S.K. has served as a consultant for Eisai, Novo Nordisk, Orexigen, and Takeda. K.F. has served as a consultant, speaker, and advisory board member for Novo Nordisk and Orexigen and has received research funding from Eisai.

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