

Role of glucagon-like peptide 1 receptor agonists in management of obesity

Diana Isaacs, Pharm.D., BCPS, BC-ADM, CDE, Chicago State University, Chicago, IL, and Oak Lawn VA Clinic of Edward Hines Jr. VA Hospital, Oak Lawn, IL.

Lalita Prasad-Reddy, Pharm.D., M.S., BCPS, BCACP, Chicago State University, Chicago, IL, and Rush University Medical Center, Chicago, IL.

Sneha Baxi Srivastava, Pharm.D., BCACP, Chicago State University, Chicago, IL, and ACCESS Community Health Network, Chicago, IL.

Purpose. Published data on the weight loss effects of glucagon-like peptide 1 (GLP-1) receptor agonists are reviewed, with a focus on data from clinical trials.

Summary. Obesity is a significant health problem in the United States (an estimated 69% of U.S. adults are overweight and nearly 35% are obese), and few drugs have proven safety and efficacy as adjuncts to lifestyle modification for weight management. GLP-1 receptor agonists are used for glycemic control in patients with type 2 diabetes and have been studied for their weight loss effects in patients with and without diabetes; these agents produce weight loss benefits through their effects on satiety and gastric emptying. In December 2014, the liraglutide product Saxenda (Novo Nordisk) became the first GLP-1 receptor agonist approved by the Food and Drug Administration (FDA) for use in long-term weight management. Results of clinical trials that evaluated the effects of GLP-1 receptor agonist therapy on weight and body mass index indicated outcomes comparable or superior to those achieved with the use of other antiobesity agents. As a class, GLP-1 receptor agonists have a generally more favorable safety profile than several other antiobesity agents; transient, mild-to-moderate gastrointestinal symptoms were the most frequently reported adverse effects in clinical trials.

Conclusion. Originally marketed for glycemic control in type 2 diabetes, GLP-1 receptor agonists have been found effective for weight reduction in patients with and without type 2 diabetes. Liraglutide is currently the only GLP-1 receptor agonist approved by FDA for obesity treatment.

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Obesity is a significant health problem in the United States. Many drugs used to treat obesity have adverse-effect profiles that limit their long-term use. Several drugs have been taken off the market due to safety concerns and limited long-term efficacy.¹ Glucagon-like peptide 1 (GLP-1) receptor agonists are used in patients with type 2 diabetes to improve glycemic control and confer significant weight loss benefits that seem to be sustained beyond the first few months of therapy.² Additionally, GLP-1 agonists have positive effects on other cardiovascular risk factors, including blood pressure and lipid panel values, which are often abnormal

in overweight or obese patients.³ The liraglutide product Saxenda (Novo Nordisk) is the most recently approved agent for chronic weight management and is the first GLP-1 receptor agonist approved by the Food and Drug Administration (FDA) for this indication.⁴ GLP-1 agonists offer a novel treatment option that may be safer and better tolerated than the available alternatives. Other GLP-1 agonists have also been studied for their effects on weight loss in patients with or without diabetes.

Obesity prevalence and clinical guidelines

During the period 2011–12, 78.6

Address correspondence to Dr. Isaacs (dianamisacs@gmail.com).

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million U.S. adults 20 years of age or older (34.9% of that age group) were considered to be obese. Obesity rates are highest in non-Hispanic blacks, with 47.8% of this population considered to be obese, followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%).⁵ Adults between the ages of 40 and 59 have a higher rate of obesity (39.5%) than other age groups. Obesity is associated with many comorbid conditions, including type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, metabolic syndrome, liver disease, depression, and osteoarthritis. Evidence suggests that reducing weight in obese patients can improve or prevent these comorbidities.⁶

Clinical guidelines suggest screening adults for obesity at least annually to reduce the risk of obesity-related comorbidities.⁷ Several guidelines define an overweight patient as having a body mass index (BMI) of 25.0–29.9 kg/m², while obesity is defined by a BMI of ≥ 30 kg/m².^{7,8} Clinicians should be aware of the potential limitations of BMI assessment in this context. BMI is a crude measurement and is often not the best indicator of obesity outcomes, as it does not take into account bone mass, distribution of fat, or muscle mass.^{9,10} Thus, BMI measurement in conjunction with an analysis of body fat percentage is the optimal method of establishing obesity. Nonetheless, in patients with an elevated BMI, guideline recommendations are to treat existing comorbidities aggressively because of the increased risk of cardiovascular disease.⁷ First-line therapy should be a nonpharmacologic approach of intensive caloric reduction and enhanced physical activity in conjunction with behavioral therapy for six months, collectively known as a comprehensive lifestyle modification.^{7,8} In clinical trials, implementation of a comprehensive lifestyle modification regimen yielded mean weight reductions of approximately 8 kg, which translated to 5–10% of baseline weight on average.⁷ Lifestyle modifi-

KEY POINTS

- Nearly all clinical trials and meta-analyses of GLP-1 receptor agonists demonstrated weight loss as a primary or secondary treatment outcome. Exenatide and liraglutide are the most-studied agents in the class.
- Compared with exenatide and liraglutide, albiglutide and dulaglutide typically have lesser weight loss effects, possibly due to their larger structure and more difficulty crossing the blood-brain barrier.
- Relative to other agents approved for obesity treatment, as a class GLP-1 receptor agonists have a more benign safety profile. The most common adverse effects are gastrointestinal symptoms, injection-site reactions, and hypoglycemia. Adverse effects are generally more likely with higher doses and dissipate with extended use.
- Liraglutide is the first GLP-1 receptor agonist approved in the United States for chronic weight management. Liraglutide offers advantages over other obesity agents, including more sustained weight loss and fewer adverse effects. Studies of long-term cardiovascular outcomes with liraglutide use are underway.

cations should be employed as the first mode of therapy because even a weight loss of 3–5% from baseline can drastically reduce cardiovascular risk.^{3,9} Nonetheless, lifestyle modifications are often ineffective for maintaining longstanding weight loss.^{9,11} Furthermore, patients in primary care environments often do not ex-

perience the same degree of success as patients in clinical trials.¹² Because the main goal of a weight loss regimen should be to decrease cardiovascular risk, pharmacotherapy can be recommended as an adjunct to lifestyle interventions in patients with a BMI of ≥ 30 kg/m² regardless of health history or those with a BMI of >27 kg/m² and one additional cardiovascular risk factor, such as diabetes, hypertension, or hyperlipidemia.^{7,8} Clinical guidelines do not suggest a preferred pharmacotherapeutic agent but instead state that treatment choice should be guided by the risks and benefits of therapy, with treatment implemented only after behavioral options have failed to produce sufficient improvements.^{7,8} There are currently five FDA-approved single-agent and combination therapies for the management of obesity in the United States: lorcaserin, orlistat, phentermine–topiramate, bupropion–naltrexone, and liraglutide. Differences between these agents in mechanism of action, dosing, weight loss effects, and adverse effects are summarized in Table 1.

All pharmacotherapeutic options should be used as adjuncts to low-calorie diets, as adherence and weight loss are increased with a combination treatment approach.⁷ Yet, widespread use of pharmacologic agents for obesity is limited by a number of factors. First, patients experience only an additional 5–10% weight loss when medication therapy is combined with lifestyle modifications.⁹ Second, many agents are associated with clinically significant weight loss in the first three months of therapy but are not effective in maintaining long-term weight loss. Third, concerns regarding the safety and adverse effects of weight loss agents, such as hepatotoxicity, increased rates of cardiovascular events, and carcinogenesis, may preclude their use¹³; this was the case with previously marketed pharmacologic agents for obesity, including a combination product containing fenfluramine and phentermine (commonly known as fen-phen) and sibutramine.¹

Table 1. Comparative Data on FDA-Approved Pharmacotherapies for Obesity^{1,9,11,13,14,a}

Drug (Brand Name[s])	Mechanism(s) of Action	Weight Loss Effects	Dosing	Adverse Effects and Toxicity	Clinical Considerations
Lorcaserin (Belviq)	Selective serotonin 2C receptor antagonism leading to reduced appetite	Modestly effective; mean weight reduction ~3.2 kg after 1 yr	10 mg orally twice daily	Adverse effects: headache, nausea, fatigue, dizziness Potentially serious toxicities: valvular heart disease, psychiatric changes, cognitive impairment	Approved for long-term management of obesity
Orlistat (Xenical, Alli)	Gastrointestinal lipase inhibition that limits fat absorption	Modestly effective; mean weight reduction ~3% from baseline after 1 yr	60–120 mg orally three times daily with fatty meals	Adverse effect: steatorrhea Potentially serious toxicities: renal failure, hepatotoxicity, pancreatitis, precancerous colon lesions	Patients experience improvements in cholesterol, blood pressure, and glucose values; available in prescription (120 mg/dose) and nonprescription (60 mg/dose) formulations
Phentermine–topiramate (Qsymia)	Phentermine stimulates sympathetic nervous system, resulting in decreased food intake and expenditure; topiramate increases energy expenditure and decreases body's ability to absorb nutrients	Effective; mean weight reduction ~9% from baseline (8 kg) at 1 yr	Available in 4 fixed-dose combinations: recommended dose is phentermine 7.5 mg with topiramate 46 mg orally once daily	Adverse effects: parosmia, headache, constipation, upper respiratory infection, dizziness, insomnia, depression, irritability Potentially serious toxicities: cardiovascular effects, teratogenic risk (topiramate)	Approved for long-term treatment of obesity; dropout rates due to adverse events as high as 19% in some clinical trials; not recommended for use in patients with recent cardiovascular or cerebrovascular disease; potential for addiction (phentermine)
Bupropion–naltrexone (Contrave)	Bupropion inhibits reuptake of dopamine and norepinephrine, thereby reducing appetite and increasing energy expenditure; naltrexone blocks opioid receptors	Modestly effective; mean weight reduction ~5% after 1 yr	Bupropion 360 mg extended release with naltrexone 32 mg orally adjusted to twice daily	Adverse effect: headache Potentially serious toxicity: lowering of seizure threshold	May result in improvements in HbA _{1c} and cholesterol values; avoid use with opioids

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Table 1. Comparative Data on FDA-Approved Pharmacotherapies for Obesity^{1,9,11,13,14,a}

Drug (Brand Name[s])	Mechanism(s) of Action	Weight Loss Effects	Dosing	Adverse Effects and Toxicity	Clinical Considerations
Liraglutide (Saxenda)	GLP-1 receptor agonism at satiety center of brain, resulting in slowed gastric emptying	Modestly effective; mean weight reduction ~3.63–5.00 kg at 1 yr	3 mg subcutaneously once daily	Adverse effects: nausea, vomiting, gastrointestinal symptoms, possible hypoglycemia Potentially serious toxicities: pancreatitis, medullary thyroid carcinoma	May result in improvement of other metabolic parameters, including blood glucose, lipids, and blood pressure; in patients taking oral antidiabetes medications or insulin, may increase risk of hypoglycemia

^aFDA = Food and Drug Administration, HbA_{1c} = glycosylated hemoglobin, GLP-1 = glucagon-like peptide 1.

GLP-1 and GLP-1 receptor agonists

GLP-1 is an endogenous hormone produced mostly by enteroendocrine L cells within the ileum, small intestine, and colon in response to dietary intake.² Plasma levels of GLP-1 increase within minutes of eating. GLP-1 stimulates insulin secretion from pancreatic β cells, decreases glucagon secretion from pancreatic α cells, decreases hepatic gluconeogenesis, and improves insulin sensitivity.¹⁵ Tissues within the cardiovascular system, central nervous system, and gastrointestinal system also contain GLP-1 receptors, and GLP-1 is known to delay gastric emptying and promote satiety.¹⁵ GLP-1 crosses the blood-brain barrier and, within the hypothalamus, affects appetite regulation by influencing satiety signals. There is also evidence of GLP-1 effects on energy expenditure that favor oxidation of fat versus carbohydrates.²

GLP-1 receptor agonists produce high levels of GLP-1, above the normal levels. They mimic the actions of endogenous GLP-1 in a glucose-dependent manner; therefore, there is a low risk of treatment-related hypoglycemia. Due to pharmacokinetic and pharmacodynamic differences among GLP-1 receptor agonists, effects on blood glucose, rates of adverse effects, and administration recommendations vary by agent. Agents within this class are administered as subcutaneous injections¹⁶ and approved for the treatment of type 2 diabetes due to their ability to reduce glycosylated hemoglobin (HbA_{1c}) values.¹⁷

In clinical trials, almost all GLP-1 receptor agonists were demonstrated to result in weight loss in addition to glucose lowering in patients with type 2 diabetes. Currently, there are five GLP-1 agonists available on the U.S. market (and a sixth agent available in Europe) that are approved for use in managing type 2 diabetes. The first GLP-1 receptor agonist introduced was exenatide (Byetta, AstraZeneca), which was approved by FDA in 2005 and is administered twice daily. The

liraglutide product Victoza (Novo Nordisk), given as a once-daily injection, was approved by FDA in 2010. The other U.S.-marketed GLP-1 receptor agonists, all administered via once-weekly injection, are the long-acting exenatide product Bydureon (AstraZeneca), approved in 2012; and dulaglutide (Trulicity, Eli Lilly and Company) and albiglutide (Tanzeum, GlaxoSmithKline), both approved in 2014. Lixisenatide (Lyxumia, Sanofi) is a once-daily GLP-1 receptor agonist available in Europe.¹⁶ Phase III clinical trials evaluating the once-weekly GLP-1 receptor agonist semaglutide (Novo Nordisk) were completed in September 2015.¹⁸ Comparative data on the weight loss effects of GLP-1 receptor agonists are presented in Figure 1.

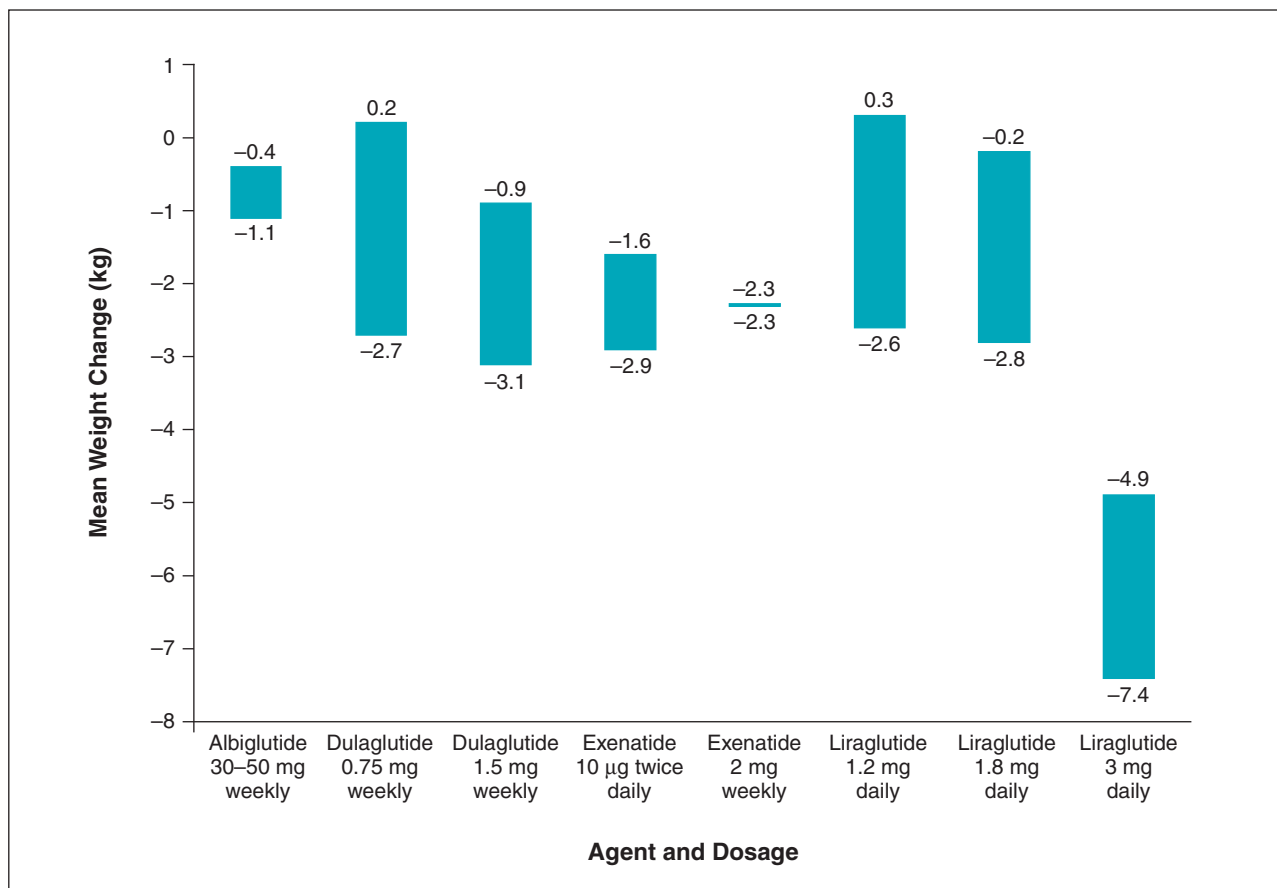
Although the mechanism of action by which GLP-1 receptor agonists bring about weight loss is not fully understood, the weight loss effects observed in patients with type 2 diabetes have led to research on the use of these agents to treat obesity in patients with and without diabetes.¹⁷ With regard to the treatment of obesity, the most intensively studied GLP-1 receptor agonist is the 3-mg formulation of liraglutide, Saxenda (the other currently available liraglutide product, Victoza, is marketed in a 1.8-mg formulation). The approval of Saxenda for the treatment of obesity in December 2014 followed several randomized controlled trials demonstrating its safety and efficacy in obese or overweight patients.¹⁹⁻²¹ Both exenatide and liraglutide have been studied

for their weight effects in patients with and without diabetes; to date, the other GLP-1 receptor agonists have been studied only in patients with diabetes.

Literature review

A search of the MEDLINE database covering the period January 2000–April 2016 was performed using the following keywords in combination with the terms *obesity, body weight, and weight loss: glucagon-like peptide-1 receptor agonist, GLP-1, liraglutide, exenatide, albiglutide, dulaglutide, lixisenatide, and semaglutide*. Studies were reviewed if they were published in English and evaluated GLP-1 receptor agonist effects on body weight or BMI in humans. Relevant references from publications obtained through the search were also reviewed. Priority was

Figure 1. Ranges of weight loss values associated with use of glucagon-like peptide 1 receptor agonists by obese or overweight clinical trial participants with and without type 2 diabetes for periods ranging from 24 to 56 weeks.



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given to clinical trials that evaluated GLP-1 receptor agonist effects in patients without diabetes.

Liraglutide effects in obese patients with diabetes. Liraglutide's effect on body weight was assessed in a 56-week randomized, double-blind, placebo-controlled trial involving 846 patients with type 2 diabetes who were overweight or obese and were receiving glycemic control therapy through diet and exercise alone or pharmacologic intervention with any of the following: metformin, sulfonylureas, and thiazolidinediones.²¹ Patients were randomly assigned to receive a subcutaneous injection of liraglutide 3.0 mg daily, liraglutide 1.8 mg daily (the maximum dose used for glycemic control), or a placebo and were instructed to follow a reduced-calorie diet and increase their physical activity. At the end of the study period, patients assigned to liraglutide 3.0 or 1.8 mg and placebo use had mean weight reductions from baseline of 6% (6.4 kg), 4.7% (5.0 kg), and 2.0% (2.2 kg), respectively. Weight loss was significantly better with liraglutide use than with placebo use ($p < 0.01$ for both doses). Significantly more liraglutide-treated patients had a weight loss of $>5\%$, with 54.3% of patients receiving liraglutide 3.0 mg and 40.4% of those receiving liraglutide 1.8 mg achieving this goal, in comparison to only 21.4% of placebo users ($p < 0.001$ for both comparisons). Additionally, a weight reduction of $>10\%$ was achieved by 25.2% of patients receiving liraglutide 3.0 mg, as compared with 6.7% of placebo users ($p < 0.001$) and 15.9% of patients taking liraglutide 1.8 mg ($p = 0.06$ for comparison with placebo use). Relative to placebo use, liraglutide use at either dose was associated with statistically significant reductions in waist circumference, BMI, HbA_{1c} levels, and other glycemic control parameters, with the 3.0-mg dose found to be superior to the 1.8-mg dose. The most common adverse effects in this trial were gastrointestinal, including nausea (approximately 33% of patients), vomiting (approx-

mately 16% of patients), and dyspepsia (approximately 11% of patients), with the highest rates observed in patients treated with liraglutide 3.0 mg. Additionally, hypoglycemic episodes occurred more frequently with liraglutide versus placebo use. Nonetheless, the majority of adverse effects were mild in severity. This study demonstrated that liraglutide could be safely used in patients with a diagnosis of diabetes, providing multiple benefits such as weight loss, improved glucose control, and BMI reduction.

A cumulative analysis of liraglutide therapy versus placebo use or active comparator agents in patients with type 2 diabetes was performed, primarily to assess the weight effects of liraglutide 1.2 or 1.8 mg daily versus other therapies but also to evaluate endpoints such as BMI and HbA_{1c} values.²² Seven randomized Phase III trials, all at least 26 weeks in duration, were assessed. Comparators to liraglutide therapy in these trials included placebo use, exenatide, sitagliptin, sulfonylureas, thiazolidinediones, and insulin glargine. The analysis revealed that patients treated with liraglutide at either dose had greater weight loss than those who received active comparators ($p < 0.0001$ for both liraglutide doses) or a placebo ($p = 0.002$ for 1.2 mg daily, and $p < 0.0001$ for 1.8 mg daily). Weight loss with liraglutide use was significantly greater than weight loss with all active comparator drugs, with the exception of exenatide. Weight loss with liraglutide use appeared to be greater among patients with higher BMI values at baseline and among patients who received the higher liraglutide dose. Additionally, weight loss of $>5\%$ from baseline was more likely with the use of liraglutide versus other evaluated agents, again with the exception of exenatide. In this analysis, liraglutide was superior to all comparators except exenatide, providing support for the use of liraglutide or exenatide, for weight management in the context of diabetes.

Liraglutide effects in obese patients without diabetes. Liraglu-

tide's potential benefit in weight management was evaluated in several randomized controlled trials in patients without diabetes. In a 56-week double-blind study, 3731 patients who met guideline criteria for pharmacotherapeutic treatment for obesity were randomly assigned to receive either a daily subcutaneous injection of liraglutide 3.0 mg or a placebo in addition to behavioral counseling on lifestyle modifications.¹⁹ Patients were evaluated every 2–6 weeks throughout the study and were assessed for BMI, weight, waist circumference, and other cardiovascular risk biomarkers. At the end of the treatment period, patients randomly assigned to liraglutide had lost significantly more weight than patients assigned to placebo use: mean, 8.4 kg versus 2.8 kg (treatment difference, 5.6 kg; $p < 0.001$). Additionally, significantly greater percentages of liraglutide-treated patients versus placebo recipients achieved weight reduction goals; 63.2% versus 27.1% achieved weight loss of at least 5% ($p < 0.001$), and 33.1% versus 10.6% achieved weight loss of 10% or more ($p < 0.001$). Liraglutide therapy was also associated with significant improvements in cardiovascular risk biomarkers such as HbA_{1c}, fasting glucose, systolic and diastolic blood pressure, total cholesterol, and triglyceride values. As in other clinical trials including GLP-1 receptor agonists, the most commonly reported adverse effects were gastrointestinal. The rate of hypoglycemia was slightly higher with liraglutide use (1.3%) versus placebo use (1.0%), although no events required medical attention. For patients without diabetes, the use of liraglutide for the pharmacologic management of obesity provides not only weight reduction but improvements in glucose control, blood pressure, and cholesterol parameters, all of which can potentially reduce cardiovascular risk.

In the SCALE trial, liraglutide was evaluated against placebo use in a large number of adults without diabetes who met criteria for obesity pharmacotherapy ($n = 422$).²³ Individuals

who were able to achieve weight loss of 5% or more on a calorie-restricted diet during the initial run-in phase of the trial were randomly assigned to receive liraglutide 3.0 mg daily or a placebo. Diet restrictions and counseling on lifestyle modifications were continued throughout the 56-week trial period. Outcomes at the end of the trial included the mean percentage weight loss after randomization, the percentage of individuals who maintained the run-in period weight loss of at least 5% after randomization, and the percentage of individuals who achieved additional weight loss ($\geq 5\%$ of body weight) after randomization. The average weight loss during the run-in period for all study participants was 6.0%. After randomization, individuals assigned to GLP-1 receptor agonist therapy had a significantly ($p < 0.0001$) greater mean weight loss (6.2%) than placebo users (0.2%). Additionally, significantly greater percentages of liraglutide-treated individuals than placebo users were able to either maintain the run-in period weight loss of $\geq 5\%$ (81.4% versus 48.9%, $p < 0.0001$) or lose 5% or more of their randomization weight (50.5% versus 21.8%, $p < 0.0001$). Although therapy with liraglutide was associated with gastrointestinal adverse effects, such effects were typically transient. Liraglutide treatment was also associated with significantly improved cardiovascular biomarkers, further supporting the use of liraglutide in the management of obesity.

Astrup and colleagues²⁰ performed a randomized, double-blind study in which liraglutide therapy at various dosages (1.2, 1.8, 2.4, or 3.0 mg daily) was compared with placebo use as well as treatment with the gastrointestinal lipase inhibitor orlistat (120 mg three times daily) in 564 adults with a BMI of 30–40 kg/m² over a period of 20 weeks; all study participants consumed a calorie-restricted diet and engaged in increased physical activity. After 2-week run-in and 4-week dosage adjustment periods, participants were maintained on a constant dose

of liraglutide for 16 weeks. The primary endpoint was the mean change in body weight from baseline. At the end of the treatment period, individuals treated with liraglutide 1.2, 1.8, 2.4, or 3.0 mg daily had mean weight reductions of 4.8, 5.5, 6.3, and 7.2 kg, respectively, while placebo users had a mean weight reduction of 2.8 kg and orlistat recipients had a mean reduction of 4.1 kg. All evaluated doses of liraglutide were significantly more effective in reducing weight than either placebo or orlistat use. Additionally, the percentage of individuals who lost more than 5% of their baseline body weight was significantly greater with liraglutide use (61% across all treatment groups) than with placebo or orlistat use ($p < 0.0001$ for both comparisons). Liraglutide therapy was also associated with an 84–96% reduction in the prevalence of prediabetes. The most commonly reported adverse effects associated with liraglutide use were gastrointestinal.

In an extension of the study of Astrup et al.,²⁴ liraglutide's efficacy, safety, and effects in sustaining weight loss were evaluated over two years. Three hundred ninety-eight participants in the original trial entered the extension and continued their assigned therapy for an additional 32 weeks, for a total treatment period of one year, after which individuals originally assigned to liraglutide (any dose) or placebo use were switched to liraglutide 2.4 mg daily, with the dosage adjusted up to a goal of 3.0 mg daily, and completed an additional year of therapy; an additional 95 individuals who had been assigned to receive orlistat in the original trial received liraglutide at the same dosage. At the end of the two-year treatment period, the mean weight reduction with liraglutide use was approximately 3.0 kg more than that observed with orlistat use ($p < 0.001$). Compared with orlistat recipients, significantly greater percentages of liraglutide-treated individuals achieved 5% and 10% weight reductions from baseline ($p < 0.001$ for both comparisons). The mean weight

loss from baseline with liraglutide use was 7.8 kg. Liraglutide was generally well tolerated; gastrointestinal adverse effects, specifically nausea and vomiting, were the most commonly reported adverse effects and were generally mild to moderate. This study demonstrated that the positive effects of liraglutide on body weight can be sustained over two years, which is a major benefit, as many antiobesity agents lose their effectiveness over time.

The safety and tolerability of liraglutide use for weight management were evaluated in a population of adolescents (age range, 12–17 years). Males and females without diabetes who were classified as obese (a BMI value in at least the 95th percentile for age and sex and corresponding to a BMI of greater than 30 kg/m² for adults) were included. A total of 21 individuals entered the trial; 14 were randomly assigned to receive liraglutide 3.0 mg daily (after a dose-escalation period), and 7 received a placebo. After five or six weeks of treatment, there was a mean change in body weight of -0.70 kg in the liraglutide group (range, -4.2 kg to 2.84 kg); no significant treatment effects on BMI z score or glucose, HbA_{1c}, and insulin levels were observed. More research is needed to further validate these findings, especially as this was a Phase I trial with a short follow-up period and weight changes with liraglutide use were small relative to those with placebo use and were not statistically significant.

Liraglutide use has also been demonstrated to confer weight management benefits in other populations. Forty patients with polycystic ovary syndrome (PCOS) were randomly assigned to receive metformin or liraglutide or both medications over 12 weeks.²⁶ Patients receiving combination therapy had a mean \pm S.D. weight loss of 6.5 ± 2.8 kg, as compared with mean weight reductions of 3.8 ± 3.7 kg in the liraglutide group and 1.2 ± 1.4 kg in the metformin group ($p < 0.001$ for both comparisons). In an observational study including 84 overweight

or obese women with PCOS who were treated with liraglutide for 4 weeks, the mean weight loss from baseline was 9.0 kg (95% confidence interval [CI], 7.8–10.1 kg; $p < 0.0001$), with 81.7% of patients losing at least 5% of body weight.²⁷ While the sample size in this study was small, benefits of liraglutide in patients with PCOS cannot be overlooked, as weight reduction and enhancements in insulin sensitivity, both desired in patients with PCOS, were observed.

Liraglutide's effects were recently studied in 359 adults with obesity and severe obstructive sleep apnea (OSA) in the placebo-controlled SCALE Sleep Apnea randomized clinical trial, which evaluated treatment with liraglutide 3.0 mg daily for 32 weeks as an adjunct to diet and exercise interventions.²⁸ In addition to improved OSA endpoints, liraglutide produced a greater mean percentage weight loss than did placebo use (5.7% versus 1.6%, $p < 0.0001$). This study provided further evidence to support the use of liraglutide in various populations.

Liraglutide has also been studied in older adults (age range, 40–70 years) with prediabetes.²⁹ Sixty-eight overweight or obese individuals with prediabetes were randomly assigned to treatment with liraglutide 1.8 mg or placebo use for 14 weeks in addition to caloric restriction (500 kcal/day). The liraglutide group had a significantly greater mean weight loss (6.8 kg), as compared with a mean weight reduction of 3.3 kg with placebo use ($p < 0.001$). The liraglutide group also had greater reductions in blood pressure, fasting glucose, and triglyceride values. Although the sample size was small, the results were encouraging with regard to the prospects for use of liraglutide in obese adults with prediabetes.

Overall, many of the trials of liraglutide provided evidence to support its use in various obese populations without diabetes.

Exenatide effects in patients with diabetes. Exenatide was evalu-

ated in several clinical trials for its impact on HbA_{1c} values in patients with type 2 diabetes. Most of these studies included effect on body weight as a secondary outcome. In one randomized, double-blind, placebo-controlled study that included 232 patients with type 2 diabetes in 23 centers around the world, exenatide 5 µg twice daily, exenatide 10 µg twice daily (adjusted upward at 4 weeks from a dosage of 5 µg twice daily), and placebo use were compared.³⁰ At baseline, mean body weights were 85.1, 86.2, and 86.1 kg in the exenatide 5-µg, exenatide 10-µg, and placebo groups, respectively; at 24 weeks, the corresponding mean \pm S.E. weight changes were -2.8 ± 0.3 kg, -3.1 ± 0.3 kg, and 1.4 ± 0.3 kg. There was a significantly higher rate of nausea in the exenatide group, as well as a nonsignificant increase in the frequency of hypoglycemia.

There have also been many randomized placebo-controlled trials evaluating exenatide twice daily in combination with metformin, a sulfonyleurea, or a thiazolidinedione (or a combination of these oral hypoglycemics), with most trials demonstrating dose-dependent statistically significant weight loss in the exenatide groups. For example, in a study of metformin plus exenatide, 272 patients completed the triple-blind, placebo-controlled trial, and a mean weight loss of 1.6 kg was reported with use of exenatide 5 µg twice daily, as compared with a mean weight loss of 2.8 kg with use of exenatide 10 µg twice daily; both reductions were significant ($p < 0.001$) relative to the mean reduction in the placebo group.³¹ In another study, mean weight reductions of 0.6 kg (nonsignificant versus placebo) and 1.6 kg ($p < 0.05$) were reported at 30 weeks with combination regimens consisting of a sulfonyleurea and exenatide 5 or 10 µg twice daily, respectively.³² In another study that examined exenatide twice daily versus insulin glargine in patients with type 2 diabetes (uncontrolled on oral therapy), patients lost a mean of 2.3 kg with exenatide use, as compared with

a mean weight gain of 1.8 kg with insulin glargine use (difference, -4.1 kg [95% CI, -4.6 to -3.5 kg]).³³

A weekly exenatide dosing schedule has also been extensively evaluated for its effect on diabetes control, with weight being a secondary outcome. The DURATION-1 trial was a 30-week, open-label, comparator-controlled study with open-ended, uncontrolled extensions of 22 weeks to five years; results were published at 52 weeks and at five years. In the initial, 30-week assessment period, 295 patients were given exenatide at a dosage of 5 µg twice daily (subsequently adjusted to 10 µg twice daily) or 2 mg weekly; all 258 patients who entered the first extension phase received the weekly dose. At the end of 52 weeks, patients who received the 2-mg weekly dose throughout study participation had a mean weight change of -4.1 kg (95% CI, -5.3 to -2.9 kg), as compared with a mean weight change of -4.5 kg (95% CI, -5.7 to -3.3 kg) in those switched from twice daily to weekly dosing for the 22-week extension.³⁴ Among 153 patients who completed five years of exenatide therapy, the mean weight change was -3.0 kg (95% CI, -4.6 to -1.3 kg).³⁵ As the DURATION-1 trial was an open-label study, there was the potential for bias that may have influenced patients' expectations³⁴; however, the weight loss findings were similar to those in other, blinded exenatide trials.^{30–32} This trial was one of the few that provided information on long-term weight loss with exenatide use.^{34,35}

Exenatide effects in patients without diabetes. Exenatide has been evaluated for its effects on weight loss in overweight or obese adults without diabetes. In one study, 41 obese women without diabetes were included in a randomized, double-blind, placebo-controlled crossover study that examined the effects of exenatide on body weight and BMI.³⁶ Secondary outcomes included waist circumference, blood pressure, heart rate, glycemic status, and self-perceived ratings of hunger, satiety, and nausea. At the end of 16 weeks, exenatide-treated women

had lost a mean of 2.49 kg, whereas placebo recipients had a mean increase in weight of 0.43 kg ($p = 0.010$). There were no significant differences between the two groups in any of the secondary outcomes. Fifty-six percent of women in the treatment group reported nausea, as compared with 21% of placebo users. The data analysis showed exenatide effects on weight ranging from an 8% decrease in weight in 30% of women to no change in weight or a weight gain in 31% of women.

In another study, the effects of exenatide therapy plus lifestyle interventions on weight loss and glucose tolerance were evaluated over 24 weeks in 152 individuals without diabetes who were randomly assigned to treatment with exenatide 5 μg twice daily (adjusted to 10 μg twice daily at 4 weeks) or placebo use in conjunction with lifestyle modifications.³⁷ At 24 weeks, the least-squares mean \pm S.E. weight reductions were 5.1 \pm 0.5 kg and 1.6 \pm 0.5 kg in the exenatide and placebo groups, respectively ($p < 0.001$). In the 25% of study participants with impaired glucose tolerance or impaired fasting glucose at baseline, 77% and 56% of those in the exenatide and placebo groups, respectively, experienced normalization of glucose. Both groups had a reduction in caloric intake.

Exenatide was also evaluated for potential use in obese pediatric patients. Kelly and colleagues³⁸ randomly assigned 26 adolescents who were severely obese to either placebo use or exenatide therapy (10 μg twice daily) to evaluate the drug's effect on BMI. Among the 22 patients who completed the trial (12 in the exenatide group and 10 in the placebo group), there was a statistically significant change in BMI (-2.70% [95% CI, -5.02% to -0.37%]; $p = 0.03$), as well as a statistically significant change in body weight (-3.26 kg [95% CI, -5.87 to -0.66 kg], $p = 0.02$), in those treated with exenatide. Additionally, during a six-month open-label extension period, exenatide therapy was associated with a cumulative 4% decrease in BMI. Other parameters, such as blood

pressure and cholesterol levels, were measured but were not statistically different between the active treatment and placebo groups. Relative to placebo users, exenatide-treated patients had higher rates of nausea (62% versus 31%) and vomiting (31% versus 8%) and lower rates of abdominal pain (15% versus 23%) and diarrhea (8% versus 31%); most of these adverse effects were transient and considered mild or moderate. Despite a small sample size, this study demonstrated the potential for exenatide use in the adolescent population. It is interesting that exenatide's weight loss effects were significant relative to those of placebo use; in contrast, when liraglutide was studied in adolescents, the resulting weight changes were minimal and not statistically significant.²⁴ However, more research is needed, especially since exenatide and liraglutide have not been directly compared and sample sizes were small in both pertinent trials summarized here.^{24,37} Orlistat is currently the only FDA-approved medication for treatment of obesity in adolescents.⁶

Albiglutide effects in patients with diabetes. Albiglutide's effects as an adjunct to metformin therapy for type 2 diabetes were evaluated in the HARMONY series of trials, with its effects on weight evaluated as a secondary outcome. The HARMONY-3 study, the largest and longest of the HARMONY trials, included 1012 patients taking metformin who were randomly assigned to placebo use or treatment with albiglutide 30–50 mg weekly, sitagliptin 100 mg daily, or glimepiride 2–4 mg daily as add-on therapy for 104 weeks.³⁹ Albiglutide was found to be superior to placebo use and the two comparator agents for glycemic control. Rates of adverse effects were similar across all study groups, with the highest rates of nausea and diarrhea reported with albiglutide use. Patients in the albiglutide, sitagliptin, and placebo groups had mean weight reductions from baseline of 1.21, 0.86, and 1.00 kg, respectively, while patients on glimepiride had a

mean weight gain of 1.17 kg. Only the treatment difference between albiglutide and glimepiride was statistically significant ($p < 0.0001$).

In the HARMONY-7 trial, albiglutide (50 mg weekly) was compared with liraglutide (1.8 mg daily) in patients with type 2 diabetes.⁴⁰ With regard to the primary endpoint of HbA_{1c} change from baseline, albiglutide failed to meet the specified criteria for noninferiority to liraglutide. Patients treated with liraglutide experienced significantly greater weight loss over the 32-week study period (a mean of 2.19 kg versus a mean of 0.64 kg with albiglutide use, $p < 0.0001$), suggesting that liraglutide is also superior to albiglutide for weight loss.

While the HARMONY trials demonstrated benefits of albiglutide therapy for weight reduction, the amounts of weight loss reported were less than those observed with the use of liraglutide or other GLP-1 receptor agonists. Of note, albiglutide is a larger molecule than exenatide and liraglutide and is structured as a conjugate protein to extend its half-life to allow for once-weekly administration. The larger structure makes it more difficult for albiglutide to cross the blood-brain barrier and affect the satiety center⁴¹; this may explain why its weight loss effects are diminished relative to those of other agents in the same class.

Dulaglutide effects in patients with diabetes. The trials that led to the approval of dulaglutide for the treatment of type 2 diabetes were the AWARD series of trials, in which the primary outcome of interest was HbA_{1c} change from baseline with the use of dulaglutide versus other agents in patients with type 2 diabetes.⁴² Change in body weight was often included as a secondary measure. AWARD-1 was a 52-week, multicenter, parallel-group study in which patients were randomly assigned to dulaglutide 1.5 or 0.75 mg weekly, exenatide 10 μg twice daily, or placebo use in addition to metformin and pioglitazone therapy. The investigators reported that the least-squares mean \pm S.E. change in body weight at

26 weeks was -1.30 ± 0.29 kg with the use of dulaglutide 1.5 mg weekly, as compared with values of 0.20 ± 0.29 kg for dulaglutide 0.75 mg weekly, -1.07 ± 0.29 kg for exenatide 10 μ g twice daily, and 1.24 ± 0.37 kg for placebo use. Compared with placebo use, both doses of dulaglutide were statistically superior ($p = 0.001$), although patients who received the lower dose actually gained weight in the study.

Nauck et al.⁴³ studied dulaglutide (at two doses) versus sitagliptin for noninferiority and superiority for glycemic control in the AWARD-5 clinical trial, a multicenter, adaptive, double-blind, parallel-group study. After 52 weeks of treatment, the dulaglutide 1.5- and 0.75-mg groups had significantly greater weight reductions (least-squares mean \pm S.E., 3.03 ± 0.22 kg and 2.60 ± 0.23 kg, respectively) than that observed in the sitagliptin group: 1.53 ± 0.22 kg ($p < 0.001$ for both comparisons). Compared with placebo use, both doses of dulaglutide were also associated with a significantly greater reduction in body weight at 26 weeks ($p < 0.001$).

AWARD-6 compared dulaglutide 1.5 mg weekly with liraglutide 1.8 mg daily.⁴⁴ Despite a greater HbA_{1c} reduction with dulaglutide versus liraglutide (least-squares mean, 1.42% versus 1.36%), weight loss was greater with liraglutide (least-squares mean, 2.90 kg versus 3.61 kg; $p = 0.011$). All of the AWARD trials were randomized; however, the AWARD-2, AWARD-4, and AWARD-6 studies were open-label trials, which may have led to bias. Overall, the use of dulaglutide at the 1.5-mg weekly dose was consistently associated with weight loss in clinical trials. However, like albiglutide, dulaglutide is structured as a conjugate protein to extend its half-life, which may explain why it is less effective for weight loss than other GLP-1 receptor agonists.⁴¹

Lixisenatide effects in patients with diabetes. The new drug application for lixisenatide for use in managing type 2 diabetes was accepted for review by FDA in September 2015.

Various randomized clinical trials have compared the effects of lixisenatide and other diabetes medications or placebo use; although the primary outcome was HbA_{1c} reduction, weight loss was measured as a secondary endpoint. For example, the GetGoal-P trial compared lixisenatide 20 μ g daily with placebo use in patients receiving background pioglitazone therapy with or without metformin.⁴⁵ Compared with mean weight loss in the placebo group, the 0.2-kg greater mean weight reduction observed in the lixisenatide group at 24 weeks was not statistically significant. The GetGoal-X trial compared lixisenatide 20 μ g daily with exenatide 10 μ g twice daily; mean weight reductions at 24 weeks were 2.96 and 3.98 kg, respectively, with a mean between-group weight-change difference of 1.02 kg (95% CI, 0.456–1.581 kg).⁴⁶ A recently completed 26-week open-label trial investigated the effects of liraglutide 1.8 mg daily versus lixisenatide 20 μ g daily as add-on therapy in patients receiving metformin. The study findings had not been published at the time of writing, but according to an abstract presented at a 2015 European Association of Diabetes meeting, liraglutide therapy and lixisenatide therapy were associated with approximate mean weight reductions of 4.26 and 3.67 kg, respectively ($p = 0.235$); glucose and HbA_{1c} lowering were better with liraglutide.⁴⁷ Adverse effects were similar in the two groups and mostly involved gastrointestinal effects such as nausea and diarrhea. Overall, weight loss effects appear to be less with lixisenatide use than with liraglutide or exenatide use.

Meta-analyses of GLP-1 receptor agonist effects on weight.

Various meta-analyses have been conducted to summarize published data on the weight loss effects of GLP-1 receptor agonists; all currently published meta-analyses focused on exenatide and liraglutide, likely because they are the agents for which the greatest amounts of clinical trial data are available. One meta-analysis reviewed data

from 25 multicenter randomized controlled trials comparing GLP-1 receptor agonists with other diabetes agents or placebo use (or both) in adults who had a BMI of >25 kg/m² with (22 trials) or without (3 trials) type 2 diabetes.⁴⁸ The evaluated trials involved a total of 3395 participants randomly assigned to receive GLP-1 receptor agonists, with 3016 assigned to various control groups. The primary outcome in all the trials was weight loss. Secondary outcomes included changes in blood pressure, liver enzyme, and total cholesterol values in addition to adverse events. Baseline characteristics were similar across the various treatment and control groups; mean BMI values ranged from 29 to 41 kg/m², and mean patient weights ranged from 82 to 111 kg. The trials evaluated liraglutide dosages of 1.2–3.0 mg/day, exenatide dosages of 5–10 μ g twice daily, and exenatide therapy at a dosage of 2 mg once weekly. Mean body weight decreases ranged from 0.2 to 7.2 kg in the GLP-1 receptor agonist groups and were greater than those observed in the control groups (mean difference, 2.9 kg; 95% CI, 2.2–3.6 kg). Subgroup analyses showed greater weight reduction with higher doses of GLP-1 receptor agonists and slightly more weight loss in patients without diabetes than in those with diabetes (mean, 3.2 and 2.8 kg, respectively). Additionally, the GLP-1 receptor agonist groups had reductions in mean systolic blood pressure, diastolic blood pressure, and total cholesterol values. The most frequently reported adverse effects in patients receiving GLP-1 receptor agonists were hypoglycemia and gastrointestinal effects (e.g., nausea, diarrhea, vomiting), which occurred more frequently with higher doses.

Another meta-analysis evaluated 51 randomized controlled trials involving 17,521 patients and other study participants with type 2 diabetes.⁴⁹ Various doses of exenatide and liraglutide were evaluated against other diabetes agents or placebo use to determine their effects on body weight. Compared with

placebo use, treatment with exenatide 10 µg twice daily was associated with a greater mean decrease in body weight (mean difference, 1.38 kg; 95% CI, 1.03–1.74 kg), as was treatment with liraglutide 1.8 mg daily (mean difference, 1.32 kg; 95% CI, 0.43–2.22 kg). Greater weight loss was observed with GLP-1 receptor agonists than with traditional antihyperglycemic drugs such as sulfonylureas, insulin, and thiazolidinediones. Mean weight reductions ranged from 1.38 to 7.30 kg with exenatide use and from 1.40 to 3.12 kg with liraglutide use. Greater weight loss was observed with higher GLP-1 receptor agonist doses, suggesting a dose-related effect. Data on the effects of a 3.0-mg liraglutide dose were not included in this meta-analysis.

Another meta-analysis evaluated data from studies to determine the effects on weight and blood pressure of exenatide at dosages of 5 µg twice daily to 2 mg weekly and liraglutide at dosages of 0.6–3.0 mg daily in adults with and without diabetes.⁵⁰ Studies were included only if they entailed the use of a non-GLP-1 receptor agonist comparator and were longer than 12 weeks in duration. In total, 33 trials were included, with a total of 7258 individuals in the meta-analysis population receiving a GLP-1 receptor agonist and 5492 receiving a comparator agent; 8% of the population did not have diabetes. Relative to treatment with non-GLP-1 receptor agonist comparators, GLP-1 receptor agonist therapy was associated with a greater loss (weighted mean difference, 2.56 kg; 95% CI, 2.00–3.12 kg). However, comparisons were not made between lower and higher doses of GLP-1 receptor agonists or between individuals with and without diabetes.

Overall, results of these meta-analyses suggest that the GLP-1 receptor agonists exenatide and liraglutide are effective interventions for overweight patients with or without diabetes.

A GLP-1 receptor agonist in the pipeline. Semaglutide is a once-weekly GLP-1 receptor agonist that

has undergone completed Phase II and Phase III clinical trials; at the time of writing, it was not approved for U.S. marketing. Semaglutide has been studied in patients with type 2 diabetes, with weight effects evaluated as a secondary outcome. In a Phase II dose-finding study, 415 patients were randomly assigned to the use of semaglutide 0.8 or 1.6 mg weekly, liraglutide 1.8 mg daily, or placebo use.⁵¹ At 12 weeks, mean weight reductions were 3.4 kg with semaglutide 0.8 mg, 4.8 kg with semaglutide 1.6 mg, and 1.2 kg with placebo use ($p < 0.001$). The mean weight reduction was greater with semaglutide 1.6 mg weekly than with liraglutide 1.8 mg daily (a 2.6-kg between-group difference), and the percentage of patients who lost over 5% of body weight was higher with the use of semaglutide 1.6 mg than with the use of liraglutide 1.8 mg (63.6% and 14.3%, respectively). There were higher rates of gastrointestinal adverse effects and withdrawals in the semaglutide 1.6-mg group relative to the comparator groups. Overall, the trial was only 12 weeks, so it is unknown whether these weight loss effects persist over time.

Phase III trials of semaglutide are in progress, with one trial completed in September 2015. Although final results of the completed trial had not been published at the time of writing, a manufacturer-issued press release reported some data from the Phase III trial, which compared the efficacy and safety of semaglutide 1.0 mg weekly and exenatide 2.0 mg weekly in 813 patients with type 2 diabetes over 56 weeks.¹⁸ There was superior HbA_{1c} lowering with semaglutide use (a mean decrease of 1.5% versus a mean decrease of 0.9% with exenatide use) and greater weight loss (mean reductions of 5.6 and 1.8 kg, respectively); both differences were statistically significant. There was a higher rate of nausea with the use of semaglutide versus exenatide. Results of other Phase III trials are not yet published, but currently available data on glycemic control and weight

loss effects with semaglutide use look promising.

Clinical trial limitations. The clinical trials summarized above provided information regarding weight loss benefits with GLP-1 receptor agonists, with the greatest amount of supportive evidence emerging from trials of liraglutide and promising results achieved with exenatide and semaglutide as well. However, the trials had a number of notable limitations. Rates of obesity are highest among blacks and Hispanics; yet, these populations are often poorly represented in clinical trials. In the trials involving treatment with liraglutide 3.0 mg, Caucasians constituted 83–85% of the respective study populations.^{19,21} In trials targeting patients with obesity, over 75% of participants were female,^{19,20} but obesity rates are higher in men.⁵ The aforementioned meta-analysis of 25 trials of GLP-1 receptor agonist therapy found that the baseline characteristics of the study populations were generally similar across trials, including mean BMI values in the range of 29–41 kg/m²; morbidly obese patients (i.e., those with a BMI of >45 kg/m²) were often excluded, so the agents' effects on those patients are unknown.⁴⁸ Also, GLP-1 receptor agonists have been studied much more extensively in patients with diabetes than in patients without diabetes. There is also a lack of information on how GLP-1 receptor agonists compare to other weight loss agents, as most have been evaluated against placebo use or other antidiabetes agents. Only liraglutide has been directly compared to orlistat, and none have been directly compared to any other antiobesity agents. Although some of the trials summarized here lasted two years or longer,^{24,35} many were of shorter duration; thus, it is not known whether weight loss achieved with GLP-1 receptor agonist use can be sustained over longer periods, especially with cessation of therapy. Another limitation is that clinical trials usually evaluate mean weight changes, but there can be great in-

terpatient variability in weight loss.³⁶ In clinical practice, it may be difficult to know which patients will have the greatest response.

Cardiovascular safety, adverse effects, and role in therapy

GLP-1 receptor agonists and cardiovascular safety. Patients who are obese are at increased risk for cardiovascular disease and often have cardiovascular risk factors such as hypertension, type 2 diabetes, and dyslipidemia.⁶ An ideal obesity agent would exhibit cardiovascular safety and have a positive impact on cardiovascular risk factors. Thus far, trials of GLP-1 receptor agonists have indicated cardiovascular safety and the agents' potential to improve cardiovascular outcomes through reduction of weight and blood glucose, blood pressure, and cholesterol levels (albeit apparently at the expense of a slight increase in heart rate).¹⁷ A meta-analysis of 33 trials of various GLP-1 receptor agonists, including exenatide (twice daily and weekly), liraglutide, taspoglutide (an investigational GLP-1 receptor agonist that never made it to market), and albiglutide, demonstrated a statistically significant reduction in major cardiovascular events with GLP-1 receptor agonist therapy versus placebo use or treatment with other antidiabetes agents.³ Long-term cardiovascular outcomes data are limited. It is unknown how the higher dose of liraglutide in Saxenda may impact cardiovascular outcomes in comparison to the lower doses used in treating type 2 diabetes. Clinical studies to further assess the potential positive or negative impact of GLP-1 receptor agonists on cardiovascular outcomes are underway.¹⁶

Adverse effects and precautions. The most common adverse effects of GLP-1 receptor agonists are gastrointestinal and include diarrhea, nausea, and vomiting.⁴⁹ These effects are more likely to occur with higher doses of GLP-1 receptor agonists or with abrupt dose increases. Over time, these symptoms usually improve. GLP-

1 receptor agonist use was discontinued due to gastrointestinal effects in less than 5% of all clinical trial participants, although higher rates of discontinuation due to gastrointestinal effects are observed in clinical practice.⁵² GLP-1 receptor agonists are not recommended for patients with gastroparesis or any disorder that reduces gastrointestinal motility. Nausea and vomiting do not actually seem to be contributing factors in weight loss observed with GLP-1 receptor agonist use, as weight loss occurs regardless of the presence or absence of those gastrointestinal effects and is sustained after the symptoms dissipate.²

Other common adverse effects of GLP-1 receptor agonists include injection-site reactions and hypoglycemia. Although these agents rarely cause hypoglycemia alone, the risk increases when they are used in combination with hypoglycemic agents. Postmarketing reports suggest that exenatide use may be associated with pancreatitis, although a causal relationship has never been confirmed. All GLP-1 receptor agonists, with the exception of exenatide (at a dosage of 10 µg twice daily), are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple neoplasia syndrome type 2. These contraindications relate to a reported increased risk of thyroid carcinoma in GLP-1 receptor agonist-exposed laboratory mice; such a link has not been reported in humans.¹⁶

Overall place in therapy for weight loss. All pharmacotherapeutic agents for obesity, when used in conjunction with intensive lifestyle interventions, increase the likelihood that patients will have clinically meaningful weight loss.¹¹ In comparison to other pharmacotherapeutic options for obesity, GLP-1 receptor agonists offer multiple benefits. Other agents on the market are limited by modest efficacy (e.g., orlistat or lorcaserin use is associated with a mean weight loss from baseline of only 3% during the first treatment year^{11,13}) or concerns regarding adverse effects, such as the

increased cardiovascular, psychiatric, and neurologic risks associated with phentermine-topiramate or lorcaserin use.¹³ Phentermine-topiramate is often used as a first-line agent in obesity secondary to its efficacy in reducing and maintaining weight loss, with approximately 50% of patients achieving weight reductions of >10% in clinical trials.⁵³ Nonetheless, adverse effects and tolerability issues associated with this agent often lead to self-discontinuation. Additionally, the potential for addiction and teratogenic effects remain as concerns, and weight gain after discontinuation of phentermine-topiramate has been documented.¹³

Relative to other antiobesity agents, as a class GLP-1 receptor agonists have numerous characteristics that make them attractive treatment options. In clinical trials, the weight loss associated with liraglutide therapy was sustained over a period of two years²⁴; moreover, a large percentage of patients achieve weight loss of >5% or >10% from baseline, and many patients using liraglutide exhibit improvements in cardiovascular risk biomarkers.¹⁹ Furthermore, GLP-1 receptor agonists appear to be well tolerated, with gastrointestinal events (typically mild to moderate and transient) being the most frequently cited adverse effects.

The liraglutide product Saxenda is the only GLP-1 receptor agonist currently approved for the indication of weight loss. For patients with type 2 diabetes who are also overweight or obese, other GLP-1 receptor agonists may be useful in promoting glucose control and weight reduction. Compared with a daily injection of liraglutide, once-weekly treatment with agents such as dulaglutide, albiglutide, and exenatide may promote greater patient adherence. However, it appears that weight loss effects are typically less with lixisenatide, albiglutide, and dulaglutide than with liraglutide.

Liraglutide dosing and administration

Saxenda is indicated for use in combination with a reduced calorie

diet and increased physical activity for chronic weight management in adult patients who are either obese (BMI of >30 kg/m²) or overweight (BMI of >27 kg/m²) with at least one weight-related comorbidity. Saxenda is available as a 6-mg/mL disposable prefilled pen with a total quantity of 18 mg of liraglutide in 3 mL of disodium phosphate dihydrate, propylene glycol, phenol, and water for injection. The initial recommended dosage is 0.6 mg daily; the dosage should be adjusted upward weekly in 0.6-mg increments to reduce gastrointestinal adverse effects. If gastrointestinal effects persist, the dose adjustment interval can be prolonged. Additionally, if more than three consecutive doses are missed, dose escalation should be restarted from the 0.6-mg daily dosage level. There are no manufacturer-recommended dose adjustments, but Saxenda use is generally not recommended in patients with severe renal or hepatic impairment.⁴

The pen has a window with a graduated scale for checking how much liraglutide is left in the pen. At the recommended upward-adjusted dose of 3.0 mg daily, each pen will last only 6 days. Patients should be counseled to check that the liquid is clear before use and taught how to select the dose using the dial-a-dose feature. The needle should be held in the skin for six seconds to ensure that the full dose is delivered. As with other pen needles, education on proper removal and disposal is important.⁴ Pens should be refrigerated prior to first use and then kept at room temperature for up to 30 days. The medication may be injected into the subcutaneous tissue of the abdomen, thighs, or upper arms.

The clinical effectiveness of liraglutide therapy should be measured at 16 weeks. If a patient has not lost at least 4% of his or her baseline body weight, liraglutide use for weight loss should be discontinued; that recommendation is based on data from the SCALE trials indicating that patients not attaining that goal by 16 weeks were unlikely to achieve and sustain

clinically meaningful weight loss with continued treatment.^{4,23} That guidance is comparable to recommendations from obesity treatment guidelines and recommendations on dosing of other obesity agents (i.e., discontinue treatment if meaningful weight loss is not achieved after 12 weeks of therapy at the suggested maintenance dose).⁶

An FDA-required Medication Guide for liraglutide includes information about the possible risks of thyroid tumors and pancreatitis with liraglutide use.⁴

Conclusion

Originally marketed for glycemic control in type 2 diabetes, GLP-1 receptor agonists have been found effective for weight reduction in patients with and without type 2 diabetes. Liraglutide is currently the only GLP-1 receptor agonist approved by FDA for obesity treatment.

Disclosures

The authors have declared no potential conflicts of interest.

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