Journal of Pharmacy Technology
2022, Vol. 38(4) 239–246

DOI: 10.1177/87551225221092681
journals.sagepub.com/home/pmt
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Once-Weekly Semaglutide for Weight Management: A Clinical Review

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Abstract

Objective: To review the efficacy, safety, and role of the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide for chronic weight management. **Data Sources:** A literature search of PubMed/MEDLINE and Google Scholar was performed using the search terms: semaglutide 2.4, weight, and obesity. Ongoing studies of semaglutide were identified utilizing clinicaltrials.gov. **Study Selection and Data Extraction:** All English-language articles evaluating the efficacy and safety of semaglutide 2.4 mg for weight management in humans were included. **Data Synthesis:** Once-weekly injectable semaglutide 2.4 mg is indicated as an adjunct to a reduced-calorie diet and increased exercise for chronic weight management in adults with a body mass index (BMI) $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus, or dyslipidemia. Semaglutide 2.4 mg has consistently demonstrated clinically significant weight loss across all phase 3 STEP (semaglutide treatment effect in people with obesity) trials, and long-term efficacy and safety have been confirmed for up to 2 years. Gastrointestinal side effects were the most frequently reported side effects, including nausea, vomiting, constipation, and diarrhea. Safety data for semaglutide 2.4 mg were consistent with that reported previously for the GLP-1 receptor agonist class. **Conclusions:** Semaglutide 2.4 mg is a highly efficacious agent for weight management, with a safety profile similar to that of other GLP-1 receptor agonists. It is a feasible option for chronic weight management, with data for up to 2 years. It is currently the only once-weekly weight loss medication, although cost may limit its utilization.

Keywords

glucagon-like peptide 1, antiobesity agents, obesity, overweight, semaglutide, review

Introduction

Obesity is a chronic disease that places a considerable burden on affected individuals and is considered a global public health challenge.[1] Obesity can cause insulin resistance, which is associated with the development of cardiovascular and metabolic conditions, such as hypertension, dyslipidemia, type 2 diabetes mellitus, nonalcoholic fatty liver disease, and polycystic ovary syndrome.[2,3] Management of obesity through weight loss has shown to reduce the risk of developing type 2 diabetes, improve lipid profiles, and reduce blood pressure.[4] Targeting a minimum weight loss of 5% total body weight is recommended. However, weight loss of 10% or more is often desired because it is associated with increased benefits for obesity-related risk factors and diseases.[4] Recommended first-line options for weight loss include lifestyle modifications that prioritize dietary changes and increased physical activity including both aerobic and resistance training exercises.[4] Limiting caloric intake between 1200 and 1800 kilocalories (kcal) per day, and reducing kcal to ensure at least a 500 kcal deficit per day are two methods that can enhance weight loss.[4] Additionally, individuals should target a minimum of 150 minutes or more of moderate-intensity exercise spread over 3 to 5 sessions per week. As adjuncts to first-line lifestyle modifications, pharmacotherapy is available to aid patients in weight management. Before the approval of semaglutide, five medications have been commonly used: orlistat, phentermine, phentermine-topiramate, naltrexone-bupropion, and liraglutide.[5]

Semaglutide, a GLP-1 receptor agonist, was initially approved in December 2017 as an adjunct to diet and exercise for the management of type 2 diabetes at doses up to 1 mg weekly. Across the phase 3 trial program for type 2 diabetes (SUSTAIN), semaglutide consistently demonstrated clinically significant weight loss (up to -6.5 kg with 1.0 mg semaglutide).[6-12] Subsequently, semaglutide has been

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approved at a higher dose, 2.4 mg, as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in patients who have obesity, or are overweight with at least one other weight-related comorbid condition.[13] This article reviews clinical trials assessing the efficacy and safety of semaglutide at a dose of 2.4 mg for chronic weight management.

Data Sources

A literature search of PubMed/MEDLINE and Google Scholar was performed using the search terms: semaglutide 2.4, weight, and obesity. All English-language articles evaluating the efficacy and safety of semaglutide 2.4 mg for weight loss in humans were included. Ongoing studies of semaglutide were identified utilizing clinicaltrials.gov. Trials evaluating the use of semaglutide at a dose of 1.0 mg were excluded as this dose is not indicated for weight management purposes.

Pharmacology and Pharmacokinetics/ Pharmacodynamics

GLP-1 is an incretin hormone with receptors present in several areas of the body, including pancreatic alpha and beta cells, the stomach, and the central nervous system. GLP-1 is a target for weight management as it slows gastric emptying and promotes satiety, which leads to a reduction in food intake. Additionally, GLP-1 crosses the blood-brain barrier where it activates areas of the hypothalamus and prefrontal cortex and regulates feeding behavior.[14,15]

The bioavailability of semaglutide is 89% when injected subcutaneously. Peak concentrations occur 3 days after injection, and steady state is achieved by Week 5 when injected once weekly. Similar exposure was achieved in three subcutaneous administration sites: the abdomen, thigh, and upper arm. Semaglutide is greater than 99% bound to plasma albumin, which provides protection from degradation and renal clearance. Semaglutide is modified through the substitution of alanine at position 8 to protect from natural degradation by dipeptidyl-peptidase 4 (DPP-4). The elimination half-life of semaglutide is approximately 1 week; therefore, semaglutide will be present for approximately 5-7 weeks after the last dose. Semaglutide is eliminated via the urine and feces. Dosage adjustments are not required based on hepatic or renal function.[13]

Dosing and Administration

Semaglutide for weight loss should be initiated at 0.25 mg once weekly and injected subcutaneously without regard to meals. Dose escalation should occur after 4 weeks to doses of 0.5 mg, 1 mg, and 1.7 mg, and the maintenance dose of 2.4 mg. If patients do not tolerate a dose during escalation, clinicians should consider a 4-week delay in dose escalation. If patients do not tolerate the maintenance dose, the dose may be decreased to 1.7 mg for 4 weeks followed by escalation back to maintenance dosing. If patients permanently fail to tolerate maintenance dosing, semaglutide should be discontinued.[13]

Clinical Efficacy

The efficacy of semaglutide 2.4 mg is being assessed across 8 trials in the STEP program. Five of these trials have been published.[16-21] The results of STEP 5 were presented at the 2021 Annual Meeting of the Obesity Society but have not been published at the time of manuscript writing.[20] Additionally, cardiovascular benefits of semaglutide 2.4 mg are being evaluated in the SELECT trial, which is currently enrolling patients.[22] Details of these trials are shown in Table 1. Across all published trials, semaglutide demonstrated a statistically significant greater percent decrease in weight from baseline and a greater likelihood of patients losing ≥5% of their body weight when compared with either placebo or liraglutide. In each trial, all patients received lifestyle intervention(s).[16-21,23]

STEP 1 evaluated the change in body weight and weight reduction of at least 5% between semaglutide 2.4 mg and placebo in adults who were obese or overweight with at least one weight-related comorbidity and did not have diabetes. Lifestyle interventions for all patients included counseling, a reduced-calorie diet, and increased physical activity. For 68 weeks, patients treated with semaglutide on average lost 14.9% of their body weight compared to 2.4% with placebo ($p<0.001$), and 86.4% of semaglutide patients achieved weight loss of 5% or more compared to 31.5% of placebo patients ($p<0.001$).[16] STEP 2 compared the same endpoints as STEP 1 for semaglutide 2.4 mg, semaglutide 1.0 mg, and placebo in overweight or obese adults with type 2 diabetes. Lifestyle interventions were consistent with STEP 1. On average, patients treated with semaglutide 2.4 mg lost 9.64% of body weight and 68.8% of patients achieved a weight loss of 5% or more at 68 weeks. Both endpoints were found to be statistically significant compared to either semaglutide 1.0mg (6.99%, 57.1%) or placebo (3.42%, 28.5%).[17] STEP 3 evaluated semaglutide 2.4 mg and placebo when combined with intensive behavioral therapy in adults who were obese or overweight with at least one weight-related comorbidity and did not have diabetes. Intensive behavioral therapy consisted of a low-calorie diet (1,000-1,200 kcal/day) for 8 weeks followed by a hypocaloric diet (1,200-1,800 kcal/day) for the remainder of the trial; 100 minutes per week of physical activity increased by 25 minutes every 4 weeks to reach 200 minutes per week; and 30 individual visits with a registered dietitian. For 68 weeks, patients treated with semaglutide 2.4 mg on average lost 16.0% of their body weight compared to 5.7% with placebo ($p<0.001$), and 86.6% of

Table 1. Clinical Efficacy Trials of Semaglutide.

Study	Purpose	Study design	Summary of population enrolled	Summary of baseline characteristics	Efficacy outcomes	
					Percent weight change from baseline to end of treatment	Percentage of patients achieving ≥5% body weight loss at the end of treatment
STEP 1[16]	To evaluate the efficacy and safety of semaglutide 2.4 mg as compared with placebo as an adjunct to lifestyle interventions for reducing body weight	n=1961 patients; 68-week phase 3 randomized, double-blind, placebo-controlled trial; multicenter study performed in 16 countries	Adults with a BMI of 30 kg/m^2 or more, or 27 kg/m^2 or more with at least 1 weight-related comorbidity; patients with diabetes were excluded	Female: 74.1% White: 75% Mean age: 46 years Mean body weight: 105.3 kg Mean BMI: 37.9 kg/m^2	-14.9% with semaglutide 2.4 mg vs. -2.4% in the placebo (estimated treatment difference, -12.4%; 95% CI, -13.4 to -11.5; p<0.001)	86.4% of patients treated with semaglutide 2.4 mg vs. 31.5% in the placebo group (p<0.001)
STEP 2[17]	To evaluate the efficacy and safety of once-weekly SQ semaglutide 2.4 mg vs. semaglutide 1.0 mg and placebo for weight management in adults with overweight or obesity, and type 2 diabetes.	n=1210 patients; 68-week phase 3 randomized, double-blind, double-dummy, placebo-controlled, multicenter superiority study performed in 12 countries	Adults with at least 1 unsuccessful dietary effort to lose weight, with a BMI of ≥27 kg/m^2 and HbA_{1c} of 7-10% and had been diagnosed with T2DM >180 days before screening, managed with diet and exercise alone or treated with stable doses of up to 3 oral glucose-lowering agents (metformin, SU, SGLT-2 inhibitors, or TZDs) for at least 90 days before screening	Female: 49.5% White: 62.1% Mean age: 55 years Mean body weight: 99.8 kg Mean BMI: 35.7 kg/m^2 Mean duration of diabetes: 8 years	-9.6% with semaglutide 2.4 mg and -3.4% with placebo (estimated treatment difference, -6.2%; 95% CI, -7.3 to -5.2; p<0.0001). -7.0% with semaglutide 1.0 mg (estimated treatment difference for semaglutide 2.4 mg vs. semaglutide 1.0 mg, -2.7%; 95% CI, -3.7 to -1.6; p <0.0001)	68.8% of patients treated with semaglutide 2.4 mg vs. 28.5% with placebo (OR, 4.88; 95% CI, 3.58-6.64; p<0.0001) or 57.1% of patients treated with semaglutide 1.0 mg (OR, 1.62; 95% CI, 1.21-2.18; p=0.0012)
STEP 3[18]	To evaluate the effects on body weight and cardiometabolic risk factors of adding SQ semaglutide 2.4 mg to intensive behavioral therapy.	n=611; 68-week phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted in the United States. All participants in this trial received a low-calorie diet (1000-1200 kcal/day) for the first 8 weeks, followed by a hypocaloric diet (1200-1800 kcal/day) for the remainder of the 68 weeks. All participants were also provided with 30 individual intensive behavioral therapy visits with a registered dietitian over the 68-week trial period.	Adults with 1 or more unsuccessful dietary efforts to lose weight, and had either BMI ≥27 kg/m^2 with at least 1 weight-related comorbidity, or BMI ≥ 30 kg/m^2. Patients with diabetes were excluded.	Female: 81% White: 76.1% Mean age: 46 years Mean body weight: 105.8 kg Mean BMI: 38 kg/m^2	-16.0% with semaglutide vs. -5.7% with placebo, both combined with intensive behavioral therapy and meal replacements (treatment difference, -10.3%; 95% CI, -12.0 to -8.6; P<0.001)	86.6% of patients treated with semaglutide vs. 47.6% in the placebo group (OR, 6.1; 95% CI, 4.0 to 9.3; p<0.001)
STEP 4[19]	To compare the effect of continuing once-weekly treatment with SQ semaglutide 2.4 mg vs. switching to placebo, both with lifestyle intervention, on body weight in participants with overweight/obesity who reached a semaglutide treatment dosage of 2.4 mg during an initial 20-week run-in	n=902; 68-week, phase 3 randomized, double-blind, placebo-controlled withdrawal study conducted in 10 countries	Adults with at least 1 self-reported unsuccessful dietary effort to lose weight and with a BMI of ≥27 kg/m^2 with at least 1 weight-related comorbidity, or BMI ≥ 30 kg/m^2. Patients with diabetes were excluded.	Female: 79% White: 83.7% Mean age: 46 years Mean body weight: 107.2 kg Mean BMI: 38.4 kg/m^2	From Week 20 to Week 69, -7.9% with continued semaglutide vs. +6.9% in those switched to placebo (treatment difference, -14.8%; 95% CI, -16.0 to -13.5; p<0.001). From Week 0 to Week 68, -17.4% with continued semaglutide vs. -5.0% with placebo (treatment difference, -12.4%; 95% CI, -13.7 to -11.0).	From Week 0 to Week 68, 88.7% with continued semaglutide vs. 47.6% with placebo.
STEP 5[20]	To evaluate the efficacy and safety of semaglutide 2.4 mg as compared with placebo as an adjunct to lifestyle interventions for reducing body weight over a 2-year period	n= 304; 104-week phase 3b randomized, double-blind, placebo-controlled, multicenter clinical trial	Adults with a BMI of 30 kg/m^2 or more, or 27 kg/m^2 or more with at least 1 weight-related comorbidity; patients with diabetes were excluded.	Female: 78% White: 93.1% Mean age: 47 years Mean body weight: 106 kg Mean BMI: 38.5 kg/m^2	-15.2% with semaglutide vs. -2.6% with placebo (estimated treatment difference, -12.6%; 95% CI, -15.3, -9.8; p<0.0001).	77.1% of patients treated with semaglutide vs. 34.4% of those treated with placebo (p<0.0001)
Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomized, double-blind, placebo and active-controlled, dose-ranging, phase 2 trial[23]	To evaluate the weight-loss efficacy and safety of semaglutide given once daily for 52 weeks at different doses (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, and 0.4 mg daily) in individuals with obesity compared to both an active control (liraglutide 3.0 mg) and an placebo	n=957; randomized, double-blind, placebo and active-controlled, multicentre, parallel group, dose-ranging, phase 2 trial.	Adults without diabetes and a BMI of 30 kg/m^2 or more not of endocrine etiology and have undergone at least 1 previous unsuccessful nonsurgical weight-loss attempt and been free from major depressive symptoms	Female: 65% White: 73% Mean age: 47 years Mean body weight: 111.5 kg Mean BMI: 39.3 kg/m^2	Mean weight reductions with semaglutide ranged from -6% with 0.05 mg to -13.8% with 0.4 mg vs. -7.8% for those receiving liraglutide and -2.3% for those receiving placebo.	Among participants still receiving semaglutide at Week 52, 60-91% had a weight loss of 5% or more depending on dose vs. 72% receiving liraglutide and 23% receiving placebo.
STEP 8[21]	To compare once-weekly semaglutide 2.4 mg vs once-daily liraglutide 3.0 mg for weight management in adults with overweight or obesity to rigorously assess differences in efficacy and safety	n= 338; 68-week phase 3b randomized, open-label trial conducted in the United States	Adults without diabetes with a BMI of 30 kg/m^2 or more, or 27 kg/m^2 or more with 1 or more weight-related comorbidity	Female: 78.4% White: 73.7% Mean age: 49 years Mean body weight: 104.5 kg Mean BMI: 37.5 kg/m^2	-15.8% with semaglutide vs. -6.4% with liraglutide (difference: -9.4% [95% CI: -12 to -6.8]; p<.001).	87.2% of patients treated with semaglutide vs. 58.1% treated with liraglutide (exploratory endpoint). 70.9% of patients treated with semaglutide achieved ≥10% body weight loss vs. 25.6% with liraglutide (secondary endpoint; p<.001)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SGLT-2, Sodium-glucose Co-transporter 2; SQ, subcutaneous; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; and TZD, thiazolidinediones.

semaglutide patients achieved weight loss of 5% or more compared to 47.6% of placebo patients ($p<0.001$).[18] STEP 4 evaluated the impact of semaglutide 2.4 mg for maintenance of weight loss after discontinuation of semaglutide. Each patient received semaglutide titrated over 16 weeks to 2.4 mg followed by 4 weeks of semaglutide 2.4 mg for a total of 20 weeks of semaglutide therapy. Patients were then randomized to either continue semaglutide therapy or replace therapy with placebo. Lifestyle interventions as described in STEP 1 were provided to both groups. For 68 weeks, patients who continued semaglutide therapy saw an additional -7.9% mean weight loss from weeks 20 to 68 compared to a mean weight gain of 6.9% in patients switched to placebo ($p<0.001$).[19] In the last placebo-controlled trial with available results, STEP 5 evaluated the change in body weight and weight reduction of at least 5% between semaglutide 2.4 mg and placebo in adults who were obese or overweight with at least one weight-related comorbidity and did not have diabetes for a period of 2 years. Described lifestyle interventions appear similar to STEP 1. For 104 weeks, patients treated with semaglutide on average lost 15.2% of their body weight compared to 2.6% with placebo ($p<0.0001$), and 77.1% of semaglutide patients achieved weight loss of 5% or more compared to 34.4% of placebo patients (p value not reported).[20]

Two published trials directly compare semaglutide to liraglutide; another GLP-1 receptor agonist indicated for weight loss. In a phase 2 trial, daily doses of semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg) were compared to liraglutide 3.0 mg daily or placebo. All participants received nutritional and physical activity counseling every 4 weeks. For 52 weeks, all doses of semaglutide showed statistically greater mean weight loss (-6.0%, -8.6%, -11.6%, -11.2%, and -13.8% listed, respectively, to doses above) compared to placebo (-2.3%). However, only doses of 0.2 mg or more showed statistically greater mean weight loss when compared to liraglutide 3.0 mg (-7.8%).[23] In the STEP program, STEP 8 confirmed the results of this phase 2 trial. Adult patients who were obese or overweight with at least one weight-related comorbidity and without diabetes were randomized to either weekly semaglutide 2.4 mg, daily liraglutide 3.0 mg, or a matching placebo. For 68 weeks, patients treated with semaglutide lost an average of 15.8% body weight compared to 6.4% with liraglutide ($p<0.001$). Secondary endpoints also showed patients were more likely to achieve 10%, 15%, or 20% weight loss with semaglutide compared to liraglutide (all $p<0.001$).[21]

Adverse Effects, Precautions/ Contraindications, and Interactions (Safety)

Consistent with prior trials of semaglutide, results of the STEP program show gastrointestinal disorders are the most frequently reported adverse reaction associated with semaglutide, with incidence rates of any gastrointestinal reaction (nausea, vomiting, diarrhea, or constipation) ranging from 10.3 to 82.2%.[16-21] Most reported reactions were mild-to-moderate in severity, transient in nature, and resolved without discontinuation of semaglutide (Table 2).[5,13,24-35] Rates of semaglutide discontinuation due to gastrointestinal disorders were low across the STEP trials evaluated (0.8-4.5%).[16-21]

Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC), in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) or in those with serious hypersensitivity reactions to semaglutide or its excipients.[13] Thyroid C-cell tumors were reported in rodent studies when treated with semaglutide in a dose-dependent, duration-dependent manner. In humans, it is unknown whether semaglutide causes thyroid C-cell tumors, including MTC. In evaluated STEP trials, no causation was established between the use of semaglutide and malignant neoplasms.[13,16-21]

Across the STEP trials evaluated, acute pancreatitis events were low, varying from 0% to 0.2%.[16-21] However, acute gallbladder disease was observed at higher rates in semaglutide treated patients (0.2-4.9%) than in placebo-treated patients (0.7-3.7%).[16-21] Acute kidney injury has been reported, but no significant difference was established in the STEP trials evaluated between patients treated with semaglutide and placebo.[16-21] It is believed that acute kidney injury is associated with dehydration due to severe gastrointestinal side effects.[13] Consistent with prior semaglutide trials, heart rate increases were reported in STEP trials one through four with a mean increase of 1-4 beats per minute.[13,36]

Consistent with other semaglutide trials, patients with type 2 diabetes treated with semaglutide 2.4 mg experienced higher rates of diabetic retinopathy than those treated with placebo (4.0% vs. 2.7% in STEP 2).[11,17] Rapid improvements in glucose control as seen with semaglutide have been associated with a temporary worsening of diabetic retinopathy.[37] Hypoglycemia is not common unless used in conjunction with insulin secretagogues or insulin.[13]

In vitro studies have shown a low potential for semaglutide to affect CYP enzymes or inhibit drug transporters. Because semaglutide may influence the rate of gastric emptying, the absorption of concomitantly administered oral medications may be delayed.[13] There was no apparent effect on the rate of gastric emptying observed during the paracetamol absorption test with semaglutide 2.4 mg.[38] Two studies showed no clinically significant pharmacokinetic or dynamic impacts on warfarin, digoxin, atorvastatin, or metformin when taken with subcutaneous semaglutide 1.0 mg or oral semaglutide 20 mg.[39,40] Further studies should be considered to evaluate semaglutide 2.4 mg on narrow therapeutic index drugs.

Table 2. Comparison of Efficacy, Side Effects, Contraindications, and Significant Drug Interactions for Common Antiobesity Medications.

Medication	Weight reduction (% weight loss from baseline; % of patients achieving ≥5% weight loss)	Common side effects	Contraindications	Significant drug interactions	Wholesale acquisition cost (duration of therapy)	Additional notes
Semaglutide 2.4 mg[5,13,16,29]	STEP 1: -14.9%; 86.4%	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease	Personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2	Limited documented interactions, concern with narrow therapeutic index drugs	$1349.02 (28 days)	Manufacturer coupon available.
Liraglutide 3.0mg[5,24,30]	-8.0%; 63.2%	Nausea, diarrhea, and vomiting	Personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2	Limited documented interactions, concern with narrow therapeutic index drugs	$1349.02 (30 days)	Manufacturer coupon available.
Phentermine HCl/ topiramate[5,25,31]	7.5 mg/46 mg: -7.8%; 62% 15 mg/92 mg: -9.8%; 70%	Constipation, xerostomia, dysgeusia, dizziness, insomnia	Glaucoma, hyperthyroidism	MAOIs, substrates of CYP3A4 and 2C19	$199.50 (30 days)	Schedule IV. Manufacturer coupon available.
Bupropion HCl/ naltrexone[5,26,32]	-6.1%; 48%	Constipation, diarrhea, nausea, xerostomia, dizziness, insomnia, hypertension, increased heart rate	Bulimia or anorexia nervosa, seizure disorder, chronic opiate use, uncontrolled hypertension	Opioids, bupropion, MAOIs, ritonavir, lopinavir, efavirenz	$303.60 (30 days)	Manufacturer coupon available.
Orlistat[5,27,33]	-7.9%; 50.5%	Abdominal discomfort, defecation urgency, leakage of oily stools, flatulence	Cholestasis, chronic malabsorption syndrome	May impair absorption of numerous medications, particular caution with cyclosporine	$685.81 (30 days at max dose of 3 tabs per day)	Patients should be counseled to take a multivitamin, separated by 2 hours, to ensure appropriate vitamin levels are maintained. No manufacturer coupon available.
Phentermine[5,28,34,35]	7.5 mg: -5.5%; 43.3% 15 mg: -6.1%; 46.2%	Xerostomia, insomnia, dizziness, increased blood pressure, increase heart rate	History of cardiovascular disease, glaucoma, hyperthyroidism	MAOIs	Tablets: $6.80 (30 days) Capsules: $13.65 (30 days)	Schedule IV. Manufacturer coupon available.

Abbreviation: MAOIs, Monoamine oxidase inhibitors.

Relevance to Clinical Practice

Semaglutide 2.4 mg is the first once-weekly injectable medication available for weight management in overweight or obese adults. In published data from the STEP program, patients treated with semaglutide 2.4 mg consistently achieved clinically meaningful weight loss compared to both placebo and liraglutide.[16-21] Despite the lack of head-to-head trials, semaglutide 2.4 mg documented safety and efficacy for periods up to 2 years establishes it as a top option for weight management when combined with lifestyle changes. In addition to a strong efficacy and safety profile, once-weekly therapy has the potential to improve adherence over daily therapy. While this was not directly evaluated in the STEP program, trials have demonstrated improved adherence with once-weekly GLP-1 therapy for diabetes mellitus over once-daily therapy.[41,42]

Semaglutide 2.4 mg is not included in current obesity guidelines by the American Association of Clinical Endocrinologists (AACE) and the American Heart Association, American College of Cardiology, and The Obesity Society (AHA/ACC/TOS), which were published in 2016 and 2013, respectively.[4,5] In the AHA/ACC/TOS guidelines, there is limited mention of pharmacotherapy due to a paucity of FDA-approved medications at the time of development. AACE guidelines do provide a summary of literature for orlistat, lorcaserin, phentermine/topiramate ER, naltrexone ER/bupropion ER, and liraglutide 3 mg and recommendations for their use. AACE does not give preference to any individual agent, except in select patient populations based upon the side effects, precautions, and contraindications of a medication. As emphasized by the AACE guidelines, there is a lack of head-to-head comparisons of approved medications for chronic weight management. However, when compared to average weight loss seen in major clinical trials of other FDA-approved medications, semaglutide 2.4 mg consistently showed greater weight loss and a greater proportion of patients achieving 5% body weight loss in STEP program trials.[5,43] Additionally, semaglutide 2.4 mg has fewer restrictions on its use than most other FDA-approved medications, excluding orlistat and liraglutide 3 mg. Common side effects, contraindications, drug interactions, and clinical pearls for these medications are shown in Table 2.[5,13,24-35] Gastrointestinal side effects of semaglutide 2.4 mg may limit its usability in some patients. Nausea and vomiting may be reduced through appropriate patient counseling focused on consuming smaller meals more frequently.

Guidelines also recommend bariatric surgery as an option for adults with a BMI ≥40 kg/m^2, or for those with a BMI ≥35 kg/m^2 and at least one weight-related comorbidity.[4,5] To compare with semaglutide, one trial of patients who received Roux-en-Y Gastric Bypass (RYGB), sleeve gastrectomy (SG), or laparoscopic adjustable gastric banding (LAGB) showed 30.9%, 23.4%, and 13% body weight reduction at 1 year, respectively, with results being less at 5 years.[44] While efficacy can be high with bariatric surgery, it is invasive in nature and side effects and complications can be severe with few ways to reverse the procedure if any. Treatment with antiobesity medications is not permanent and allows for dosage adjustments and discontinuation of the medication. However, the availability of pharmacotherapy should not rule out bariatric surgery.

Based on available literature, semaglutide 2.4 mg is a strong addition to pharmacotherapeutic options for chronic weight management. It has shown consistent clinically significant weight loss across the STEP program, with limited major side effects or contraindications. Despite this, one barrier to its use that will continue is its cost as it is currently among the most expensive of available agents (Table 2). Clinicians who are considering prescribing semaglutide 2.4 mg should make sure to evaluate opportunities from the manufacturer to reduce the cost.

Conclusions

Semaglutide is a GLP-1 receptor agonist recently approved by the FDA for weight management at a dose of 2.4 mg once weekly in patients with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with more than one weight-related comorbidity. Semaglutide is highly efficacious, with the majority of patients experiencing clinically significant weight loss across STEP trials to date. Its efficacy and safety have been demonstrated for up to 2 years, making it an ideal option for chronic weight management, although its use may be limited by its cost.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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