Semaglutide for weight loss and cardiometabolic risk reduction in overweight/obesity

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Purpose of review
Cardiovascular disease is the most common cause of morbidity and mortality worldwide, and the risk is heightened in the presence of obesity. We review semaglutide, a drug recently approved for chronic weight management in adults with obesity or who are overweight.

Recent findings
On 4 June 2021, the US Food and Drug Administration approved semaglutide injection at 2.4 mg once weekly for chronic weight management in adults with obesity or overweight with at least one weight-related condition such as high blood pressure, type 2 diabetes mellitus, or high cholesterol. This subcutaneous injection is the first approved drug for chronic weight management in adults with general obesity or overweight since 2014. The drug is indicated for weight management in patients with a BMI of 27 kg/m^2 or greater who have at least one weight-related ailment or in patients with a BMI of 30 kg/m^2 or greater.

Summary
Semaglutide offers adults with obesity or overweight a new treatment in conjunction with a weight management program consisting of reduced calorie diet and increased physical activity.

Keywords
cardiometabolic syndrome, diabetes mellitus, glucagon-like peptide-1, obesity, overweight

INTRODUCTION

Cardiovascular disease remains the most common cause of morbidity and mortality worldwide, and the risk is significantly heightened in the presence of obesity or being overweight [1]. Obesity, classified by the American Medical Association in 2013 as a disease, is a preventable disease and the most common modifiable risk factor for several chronic diseases including cardiovascular disease [2]. Available evidence suggests that by 2030 the majority of adults will be obese and the prevalence of obesity will approach 60% in some states and not be below 35% in any state in the United States [3]. This is concordant with prior estimates showing that 57% of children 2–19 years of age in 2016 were projected to have obesity by the age of 35 years [4]. Furthermore, data projections suggest that severe obesity will affect nearly one in four adults by 2030 and become the most common BMI category among women, black non-Hispanic adults, and low-income adults [3]. This disproportionate burden among individuals in minority groups and those with low socioeconomic status will further contribute to disparities in cardiometabolic risk and consequent higher morbidity and mortality in these groups [5]. The management of obesity should be a multidisciplinary approach that includes the patient and his or her family, the primary care provider, a dietician or nutrition specialist and physical trainer. It may also require the use of pharmacological and surgical interventions in select individuals. In this article, we specifically review semaglutide, a drug recently approved for chronic weight management and its potential role in managing obesity and corpulence. The robust and sustained effects of semaglutide on glycated hemoglobin (Hb) levels and weight loss vs. placebo, as well as its safety and cardiovascular benefits makes it an attractive therapeutic agent in the treatment of type 2 diabetes [6].

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KEY POINTS

- Obesity is a preventable disease and the most common modifiable risk factor for several chronic diseases including cardiovascular disease.
- Lifestyle intervention including dietary restriction and physical exercise remains the mainstay of weight management.
- Available evidence suggests that once-weekly subcutaneous semaglutide and lifestyle intervention is associated with substantial, sustained, and clinically relevant mean weight loss in individuals with and without diabetes mellitus.
- Additional studies are indicated to assess the impact of weight loss with semaglutide on hard cardiovascular endpoints including morbidity and mortality.
- If semaglutide is made more affordable, this effective therapy will be available to more individuals with obesity and can be cost effective.

EVIDENCE REVIEW

Lifestyle intervention including dietary restriction and physical exercise is the mainstay of weight management but sustained weight loss with this strategy remains challenging [7]. Adjunctive pharmacotherapy is suggested for adults with a BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater in persons with coexisting conditions in current guidelines [8–10]. However, currently available drugs remain limited by at best modest efficacy, side effects, and cost [11] Table 1 summarizes currently available drugs for weight management. Semaglutide, a glucagon-like peptide-1 (GLP-1) analog had been previously approved, at doses up to 1 mg administered subcutaneously once weekly, for the treatment of type 2 diabetes in adults and for reducing the risk of cardiovascular events in persons with type 2 diabetes and cardiovascular disease. On 4 June 2021, the US Food and Drug Administration (FDA) approved semaglutide injection at 2.4 mg once weekly for chronic weight management in adults with obesity or overweight with at least one weight-related condition such as high blood pressure (BP), type 2 diabetes mellitus, or high cholesterol, for use in addition to a reduced calorie diet and increased physical activity.

Clinical studies

The global phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program evaluated the efficacy and safety of semaglutide administered subcutaneously at a dose of 2.4 mg once weekly in persons with overweight or obesity, with or without weight-related complications [18▪▪]. This double-blind trial enrolled 1961 adults either with a BMI at least 30 kg/m^2 or BMI at least 27 kg/m^2 in persons with at least one weight-related coexisting condition, without diabetes. The study randomly assigned participants in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, and lifestyle intervention [18▪▪]. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand which is a precise description of the treatment effect mirroring the objective of the clinical trial assessed effects regardless of treatment discontinuation or rescue interventions [18▪▪]. The mean change in body weight from baseline to week 68 was−14.9% in the semaglutide group as compared with−2.4% with placebo, with a treatment difference of −12.4 percentage points [95% confidence interval (CI), −13.4 to −11.5; $P < 0.001$]. The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group (estimated treatment difference,−12.7 kg; 95% CI, −13.7 to−11.7) and participants who received semaglutide also had a greater improvement with respect to cardiometabolic risk factors [18▪▪]. Those who received semaglutide showed greater reductions in waist circumference, BMI, and SBP and DBP compared with placebo, and had improved levels of glycated Hb, fasting plasma glucose, C-reactive protein, and fasting lipid levels. Furthermore, these participants reported greater increases in physical functioning from baseline compared with placebo. This trial reported that once-weekly subcutaneous semaglutide and lifestyle intervention was associated with substantial, sustained, and clinically relevant mean weight loss of 14.9%, with 86% of participants attaining at least 5% weight loss.

The STEP 2 trial assessed the efficacy and safety of semaglutide 2.4 mg vs. semaglutide 1.0 mg (the dose approved for diabetes treatment) and placebo for weight management in adults with overweight or obesity, and type 2 diabetes [19▪]. Patients were randomly allocated (1:1:1) to subcutaneous injection of semaglutide 2.4 mg, or semaglutide 1.0 mg, or placebo, once a week for 68 weeks, and lifestyle intervention. A total of 1210 individuals with diabetes were randomly assigned to semaglutide 2.4 mg ($n = 404$), semaglutide 1.0 mg ($n = 403$), or placebo ($n = 403$) and included in the intention-to-treat analysis [19▪]. The mean bodyweight change from baseline to week 68 was−9.6% [standard error (SE) 0.4] with semaglutide 2.4 mg compared to −7.0% (SE 0.4) with semaglutide 1.0 mg and [−3.4% (SE 0.4)] with placebo, with clinically meaningful reductions

Table 1. Currently available pharmacotherapies approved to treat overweight and obesity

Pharmacotherapy	Year approved	Mechanism and dosage	Side effects
Orlistat (Xenical) [12]	1999	A reversible inhibitor of gastric and pancreatic lipases, thus inhibiting absorption of dietary fats by 30% 120 mg 3 times daily with each main meal containing fat (during or up to 1 h after the meal); omit dose if meal is occasionally missed or contains no fat	Oily rectal leakage (4–27%), abdominal distress (≤26%), abdominal pain (≤26%), flatulence with discharge (2– 24%), bowel urgency (3–22%), steatorrhea (6–20%), oily evacuation (2–12%) Rare cases of severe liver injury have been reported Avoid taking with cyclosporine
Phentermine-topiramate (Qsymia) [13]	2012	Phentermine is a sympathomimetic amine and reduces appetite secondary to CNS effects, including stimulation of the hypothalamus to release norepinephrine Topiramate blocks neuronal voltage-dependent sodium channels, enhances $GABA_A$ activity, antagonizes AMPA/kainite glutamate receptors, and weakly inhibits carbonic anhydrase Phentermine 3.75 mg/topiramate 23 mg once daily for 14 days. Increase dose to phentermine 7.5 mg/topiramate 46 mg once daily for 12 weeks then evaluate weight loss. If 3% of baseline body weight has not been lost, discontinue use or increase dose to phentermine 11.25 mg/ topiramate 69 mg once daily for 14 days, and then to phentermine 15 mg/topiramate 92 mg once daily	Tachycardia, cognitive dysfunction, and psychiatric disturbances (mood disorders including anxiety, depression, or insomnia) may occur with use. Advised caution in patients with cardiovascular disease Do not use if patient has glaucoma or hyperthyroidism May lead to birth defects, contraindicated in pregnancy and with breastfeeding
Lorcaserin (Belviq) [14]	2012	The medication stimulates 5-HT2C receptors on the POMC neurons in the arcuate nucleus; this causes the release of alpha-MSH, which acts on melanocortin-4 receptors in the paraventricular nucleus to suppress appetite Withdrawn from market	In February 2020, the US FDA asked the manufacturer of lorcaserin to voluntarily withdraw lorcaserin from the United States market because of clinical trial data showing an increased occurrence of cancer
Naltrexone-bupropion (Contrave) [15]	2014	The exact mechanism of naltrexone/bupropion leading to weight loss are not fully understood. Effects may result from action on areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system) One tablet (naltrexone 8 mg/bupropion 90 mg) once daily in the morning for 1 week; at week 2, increase to 1 tablet twice daily administered in the morning and evening and continue for 1 week; at week 3, increase to 2 tablets in the morning and 1 tablet in the evening and continue for 1 week; at week 4, increase to 2 tablets twice daily and continue for the remainder of the treatment course	Nausea, headache, and constipation. Other adverse effects included insomnia, vomiting, dizziness, and dry mouth. May increase suicidal thoughts or actions. Do not use in individuals dependent on opioid pain medications or withdrawing from drugs or alcohol.
Liraglutide (Saxenda) [16]	2014	Liraglutide is a long-acting analog of human GLP-1 (an incretin hormone) which increases glucosedependent insulin secretion, decreases inappropriate glucagon secretion, increases B-cell growth/replication, slows gastric emptying, and decreases food intake Initial: 0.6 mg once daily for 1 week; increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily.If the patient cannot tolerate an increased dose during dose escalation,consider delaying dose escalation for 1 additional week	Gastrointestinal side effects, including nausea and vomiting, are common. Other side effects include diarrhea, low blood sugar, and anorexia May increase the chance of developing pancreatitis

Table 1 (*Continued*)

Pharmacotherapy	Year approved	Mechanism and dosage	Side effects
Imcivree (Setmelanotide) [17]	2020	MC4R agonist designed to restore impaired MC4R pathway function caused by genetic variants that occur upstream of the receptor ONLY approved for obesity due to three rare genetic conditions: POMC deficiency, PCSK1 deficiency, and LEPR deficiency confirmed by genetic testing Starting dose: 2 mg SC qDay for 2 weeks; 2 mg qDay not tolerated: Reduce to 1 mg SC qDay; if 1 mg qDay tolerated and additional weight loss desired, titrate to 2 mg qDay 2 mg qDay tolerated and additional weight loss desired: Increase to 3 mg SC qDay; if not tolerated, maintain dose at 2 mg qDay Not recommended for those with moderate, severe, or end-stage renal disease	Injection site reactions, skin darkening, nausea, disturbance in sexual arousal, and depression and suicidal ideation
Semaglutide (Wegovy) [18▪▪,19▪]	2021	Long-acting GLP-1 receptor agonist which can be administered as a once-weekly subcutaneous Week 1 through week 4: 0.25 mg once weekly Week 5 through week 8: 0.5 mg once weekly Week 9 through week 12: 1 mg once weekly Week 13 through week 16: 1.7 mg once weekly Week 17 and thereafter (maintenance dosage): 2.4 mg once weekly; if not tolerated, may temporarily decrease dosage to 1.7 mg once weekly for up to 4 additional weeks, then increase to 2.4 mg once weekly	Gastrointestinal symptoms such as nausea, diarrhea, vomiting, constipation, and abdominal pain May cause headache, fatigue In clinical studies, these adverse effects were generally mild-to-moderate and, for most patients, improved over time

Alpha-MSH, alpha-melanocortin-stimulating hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CNS, central nervous system; FDA, Food and Drug Administration; GABAa, γ-aminobutyric acid type A; GLP-1, glucagon-like peptide-1; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein subtilisin/kexin type 1; POMC, pro-opiomelanocortin; qday, every day; SC, subcutaneous.

(≥5%) reported in more than two-thirds of patients on semaglutide 2.4 mg [19▪]. Furthermore, the magnitude of weight loss achieved with semaglutide 2.4 mg in this study was greater than that seen with liraglutide and other approved antiobesity medications in similar patient populations [19▪].

The STEP 3 clinical trial evaluated the additive effects of subcutaneous semaglutide 2.4 mg, to intensive behavioral therapy, which included an initial 8-week low-calorie diet to boost total weight loss on body weight and cardiometabolic risk factors [20]. At week 68, the estimated mean body weight change from baseline was −16.0% for semaglutide vs. −5.7% for placebo [difference,−10.3% points (95% CI, −12.0 to−8.6); $P < 0.00l$]. More individuals treated with semaglutide vs. placebo lost at least 5% of baseline body weight (86.6 vs. 47.6%, respectively; $P < 0.001$) [20]. Semaglutide used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in significantly greater weight loss than placebo during 68 weeks in adults with overweight or obesity without diabetes.

Subsequently, the STEP 4 withdrawal trial was conducted to compare the effect of continuing once-weekly treatment with subcutaneous 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 once weekly during an initial 20-week run-in [21▪▪]. In this trial, 902 participants received once-weekly subcutaneous semaglutide during run-in. After 20 weeks (16 weeks of dose escalation; 4 weeks of maintenance dose), 803 participants (89.0%) who reached the 2.4-mg/week semaglutide maintenance dose were randomized (2: 1) to 48 weeks of continued subcutaneous semaglutide ($n = 535$) or switched to placebo ($n = 268$), and lifestyle intervention in both groups. With continued semaglutide, mean body weight change from week 20 to week 68 was −7.9% vs. +6.9% with the switch to placebo [difference, −14.8% points (95% CI, −16.0 to −13.5); $P < 0.001$]. Waist circumference [−9.7 cm (95% CI, −10.9 to −8.5 cm)], SBP [−3.9 mmHg (95% CI, −5.8 to −2.0 mmHg)], and SF-36 physical functioning score [2.5 (95% CI, 1.6–3.3)] also improved with continued

Table 2. Key findings from the Semaglutide Treatment Effect in People with Obesity trials

Study	Number of participants	Results	Key Message
STEP 1 [18▪▪]	1961	The mean change in body weight from baseline to week 68 was–14.9% in the semaglutide group as compared with–2.4% with placebo, with a treatment difference of–12.4% points (95% CI, –13.4 to–11.5; $P<0.001$)	In overweight or obesity participants WITHOUT diabetes, 2.4 mg of semaglutide once weekly + Lifestyle intervention was associated with sustained, clinically relevant reduction in body weight
STEP 2 [19▪]	1210	Once a week semaglutide 2.4 mg achieved a greater decrease in mean body weight [–9.6% (SE 0.4)] compared with semaglutide 1.0 mg [–7.0% (SE 0.4)] and placebo [–3.4% (SE 0.4)], with clinically meaningful reductions (≥5%) reported in more than two-thirds of patients on semaglutide 2.4mg	In adults with overweight or obesity, and WITH type 2 diabetes, semaglutide 2.4 mg once a week achieved a superior and clinically meaningful decrease in body weight compared with placebo
STEP 3 [20]	611	At week 68, the estimated mean body weight change from baseline was 16.0% for semaglutide + intensive behavioral therapy and initial low-calorie diet vs.–5.7% for placebo [difference,–10.3 percentage points (95% CI, –12.0 to–8.6); $P<0.001$]	Semaglutide used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in greater weight loss than placebo during 68 weeks in adults with overweight or obesity WITHOUT diabetes
STEP 4 [21▪▪]	803	With continued semaglutide, mean body weight change from week 20 to week 68 was–7.9% vs. + 6.9% with the switch to placebo [difference,–14.8 percentage points (95% CI, –16.0 to–13.5); $P<0.001$]	Overweight or obese adults WITHOUT diabetes who completed a 20-week run-in period with subcutaneous semaglutide, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks
STEP 8 [22]	338	Participants had significantly greater odds of achieving 10% or more, 15% or more, and 20% or more weight loss with semaglutide vs. liraglutide [70.9% of participants vs. 25.6% (odds ratio, 6.3 (95% CI, 3.5–11.2)), 55.6 vs. 12.0% (odds ratio, 7.9 (95% CI, 4.1–15.4)), and 38.5 vs. 6.0% (odds ratio, 8.2 (95% CI, 3.5–19.1)), respectively; all $P<0.001$]	Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide, compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity resulted in significantly greater weight loss at 68 weeks

CI, confidence interval; SE, standard error; STEP, Semaglutide Treatment Effect in People with Obesity.

subcutaneous semaglutide vs. placebo (all $P<0.001$). This study suggested that maintaining treatment with subcutaneous semaglutide compared with switching to placebo resulted in continued weight loss. Table 2 summarizes key findings from the STEP trials.

Finally, the STEP 8 study compared the efficacy and adverse event profiles of once-weekly subcutaneous semaglutide, 2.4 mg, vs. once-daily subcutaneous liraglutide, 3.0 mg (both with diet and physical activity), in people with overweight or obesity [22]. This randomized clinical trial that included 338 participants, reported mean body weight change from baseline to 68 weeks was–15.8% with semaglutide vs.–6.4% with liraglutide, a significantly greater weight loss at 68 weeks.

In addition, a 72-week, double-blind phase 2 trial involving patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) of 320 patients reported that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo [23].

A recent meta-analysis analyzed percentage change in body weight for 4824 participants from five studies and reported that semaglutide is superior to placebo in weight loss, change in waist circumference, change in SBP, change in SF-36 physical functioning score, and change in IWQOL-Lite-CT physical function score [24▪]. Another meta-analysis of four trials with 3447 patients reported that once-weekly semaglutide was superior to placebo in terms of the percentage change and absolute change in body weight and improved other cardiometabolic risk factors and health-related quality of life [25].

These data suggest that semaglutide may be a safe and effective therapy in treating patients with obesity or overweight.

CONCLUSION

Available data suggest a marked weight loss with semaglutide among individuals both with and without diabetes mellitus, and along with known beneficial effects of GLP-1 receptor agonists on cardiovascular outcomes among those with diabetes, this drug becomes an attractive option for obese or overweight individuals. Based on currently available evidence, on 4 June 2021, the US FDA approved semaglutide injection at 2.4 mg once weekly for

chronic weight management in adults with obesity or overweight with at least one weight-related condition such as high BP, type 2 diabetes mellitus, or high cholesterol, for use in addition to a reduced calorie diet and increased physical activity. The drug is indicated for weight management in patients with a BMI of 27 kg/m^2 or greater who have at least one weight-related ailment or in patients with a BMI of 30 kg/m^2 or greater. Furthermore, adults with overweight or obesity completing a 20-week run-in period, maintaining treatment with subcutaneous semaglutide compared with switching to placebo resulted in continued weight loss and is therefore recommended [21▪▪]. Only 2.4 and 2.2% of participants receiving continued semaglutide and placebo, respectively, discontinued treatment because of adverse events with one death reported in each group attesting to the safety of maintenance therapy. Lee *et al.* [26▪] assessed cost-effectiveness of pharmacotherapy and lifestyle intervention in the treatment of obesity and reported that semaglutide was the most effective strategy in the 3-and 5-year time horizons, with total quality-adjusted life years (QALYs) of 2.224 and 3.711, respectively but, the incremental cost-effectiveness ratios were prohibitively high at $1437 340/QALY after 3 years and $576931/QALY after 5 years its high price. If semaglutide is made more affordable, this effective therapy will be available to more individuals with obesity and can be cost effective. Additional studies are indicated to assess the impact of semaglutide on cardiovascular morbidity and mortality among individuals with obesity, and is being examined in a large 17,500 participant clinical trial, the Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) (Clinical-Trials.gov Identifier: NCT03574597) study.

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Conflicts of interest

A.C.M., S.C., and D.M. declare that they have no conflict of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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