REVIEW

Clinical Insight on Semaglutide for Chronic Weight Management in Adults: Patient Selection and Special Considerations

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Abstract: Losses of 5–10% or more of initial body weight are associated with improvements in obesity-related comorbidities. However, attaining and sustaining this level of weight loss is challenging. The novel anti-obesity medication semaglutide 2.4 mg injected subcutaneously once weekly as an adjunct to a reduced-calorie diet and physical activity helps patients achieve average losses of 9.6–17.4% of initial body weight at week 68, as well as improvements in cardiometabolic and psychosocial indices. Despite these average benefits, prescribers should carefully assess the suitability of patients for this medication. In this paper, we discuss considerations for the selection of individuals who are candidates for semaglutide and special considerations related to the use of this medication. These include its efficacy and safety, as well as its contraindications, potential adverse effects, management of comorbidities and drug interactions, insurance coverage and cost, and patient preferences.

Keywords: GLP-1, obesity, pharmacotherapy, semaglutide, weight loss

Introduction

Intensive lifestyle intervention (ILI) that includes counseling on behavioral, physical activity, and dietary strategies is the first-line treatment for obesity.[1,2] In clinical research trials, ILI produces losses of 7–8% of initial weight at 1 year.[3–5] Approximately 46[6]–68%[7] of participants achieve a ≥5% initial weight loss, which is associated with clinically significant health benefits.[4,8,9] However, translation and implementation of ILI into clinical and community settings has been challenging due to time, knowledge, and resource limitations.[10] ILI delivered in these settings is associated with more modest average weight losses of 4–5%[11,12] with 36% of participants achieving a ≥5% initial weight loss.[12] While a ≥5% initial weight loss is associated with health benefits, larger weight losses produce even greater improvements in health parameters,[8,9,13,14] and some obesity-related conditions, such as obstructive sleep apnea and non-alcoholic steatohepatitis, require a 10–20% weight loss for clinical improvements.[15] Larger weight losses are also typically more congruent with patient goals and expectations for obesity treatment.[16] Weight loss reductions larger than 5% of initial weight are difficult to achieve and sustain with behavioral treatment alone.

Anti-obesity medications, when combined with lifestyle intervention, produce larger weight losses than behavioral treatment alone.[17] Guidelines and expert opinions for adult obesity treatment specify that candidates for anti-obesity medications are individuals with a body mass index (BMI) ≥30 kg/m², or a BMI ≥27 and <30 kg/m² with at least one weight-related condition (such as hypertension, dyslipidemia, or type 2 diabetes), who have not met weight-loss goals with ILI. Weight loss goals are typically considered a loss of ≥5% of initial body weight at three to six months. In East Asian countries, the BMI threshold for obesity is ≥28.0 kg/m² and for overweight is ≥24.0 kg/m².[18] In India, the BMI threshold for obesity is ≥25.0 kg/m² and for overweight is ≥23.0 kg/m².[19] The decision to begin anti-obesity medications should be personalized, considering the benefits and risks of all treatment options.

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The United States Food and Drug Administration (FDA) has approved five medications, as adjuncts to a reduced-calorie diet and increased physical activity, for chronic weight management. These include orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide. The European Medicines Agency (EMA) has approved all except phentermine/topiramate. In China, only orlistat is approved. Orlistat, phentermine/topiramate ER, naltrexone ER/bupropion ER, and liraglutide produce placebo-subtracted weight losses of 2.6 kg (orlistat) to 8.8 kg (phentermine-topiramate) at 1 year.[20] Semaglutide 1.0 mg, once-weekly, subcutaneous injection, was first approved as a treatment for type 2 diabetes in 2017. Semaglutide at a dose of 2.4 mg administered as a once-weekly, subcutaneous injection, was approved for chronic weight management by the FDA in 2021, by the UK Medicine and Health Products Regulations Agency 2021, and by the European Medicines Agency's Committee for Medicinal Products for Human Use in 2022. The average placebo-subtracted weight loss for semaglutide was 12.7 kg.[21] Semaglutide has generated much scientific, clinical, and public excitement and interest given these large weight losses. In this paper, we summarize the weight loss efficacy of semaglutide and discuss the criteria to be considered in the selection of patients who are candidates for semaglutide and special considerations related to its use in different patient populations.

Semaglutide

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that is released during a meal. Among its multifaceted functions is the ability to connect the absorption of nutrients from the gastrointestinal tract with pancreatic hormone secretion.[22] Semaglutide is a GLP-1 receptor agonist (GLP-1RA). It stimulates glucose-dependent insulin release from the pancreatic islets, reduces glucagon release, and promotes insulin secretion.[23] Semaglutide reduces appetite, stimulates satiety, and decreases ad libitum energy intake.[24] This medication should be taken on the same day each week, at any time and with or without food. To minimize gastrointestinal side effects, it is titrated up starting at 0.25 mg once a week with dose increases every 4 weeks until the full dose of 2.4 mg is reached.

Semaglutide, injected subcutaneously once weekly at doses of 1.0 and 2.0 mg for type 2 diabetes, was well studied in the SUSTAIN clinical trial program. The SUSTAIN program included nine Phase 3a clinical trials (SUSTAIN 1–6,[25–30] two trials conducted in Japan,[31,32] and one China Multi-Regional Clinical Trial[33]), and four phase 3b clinical trials (SUSTAIN 7–10[34–37]). The efficacy and safety of semaglutide 2.4 mg, once weekly subcutaneous, for chronic weight management was demonstrated in the Semaglutide Treatment Effect in People with Obesity (STEP) program.[38] The STEP program is a series of multicenter, phase 3 randomized clinical trials focused on evaluating the safety and efficacy of semaglutide 2.4 mg as a weight loss medication in patients with obesity (or a BMI of $\geq$27.0 kg/m^2 with at least one cardiovascular disease risk factor). Below we summarize the published trials of semaglutide for chronic weight management which includes STEP trials 1–6, and 8.

STEP 1

In this 68-week trial, 1961 adults without type 1 or 2 diabetes were randomly assigned in a 2:1 ratio to once weekly subcutaneous semaglutide or matching placebo.[21] Semaglutide was introduced gradually, as described earlier, such that participants began the 2.4 mg dose at the end of week 16. Every 4 weeks, participants in both groups were provided brief counseling visits with a registered dietitian (RD) who instructed them in reducing their daily energy intake by 500 kcal/d and in achieving a weekly activity goal (typically walking) of 150 minutes or more.

At week 68, semaglutide-treated participants lost an average of 14.9% of baseline weight, compared with 2.4% for those assigned to placebo. Fully 86.4% of the semaglutide group lost 5% or more on baseline weight, compared with 31.5% for placebo. Semaglutide also was superior in the percentage of participants who lost $\geq$10% (69.1 vs 12.0%), $\geq$15% (50.5 vs 4.9%), and $\geq$20% of baseline weight (32.0 vs 1.7%). Weight loss with semaglutide, compared with placebo, was associated with clinically meaningful improvements in several cardiometabolic risk factors, including waist circumference, systolic and diastolic blood pressure, and glycated hemoglobin, as well as with benefits to physical and emotional quality of life. STEP 1 was the largest randomized trial of semaglutide 2.4 mg, and its favorable safety and efficacy data were pivotal in the medication's approval by international regulatory bodies.

STEP 2

STEP 2 was a 68-week trial of 1210 adults with type 2 diabetes (ie, glycated hemoglobin of 7–10%) and overweight/obesity who were assigned in equal numbers to once-weekly semaglutide 2.4 mg, semaglutide 1.0 mg, or matching placebo.[39] Study eligibility included taking up to three oral glucose-lowering medications (ie, metformin, sulfonylureas, SGLT2 inhibitors, or thiazolidinediones) but not insulin. Participants in all three groups received the same program of diet and activity counseling provided in STEP 1.

At week 68, participants treated by semaglutide 2.4 mg, semaglutide 1.0 mg, and placebo lost a mean of 9.6, 7.0, and 3.4% of baseline body weight, respectively. Thus, the 2.4 mg dose significantly increased weight loss, compared to 1.0 mg, the latter which was originally approved for the treatment of type 2 diabetes. (The US FDA recently approved a 2.0 mg dose of semaglutide for type 2 diabetes.) Changes in HbA1c, systolic and diastolic blood pressure, and other cardiometabolic risk factors were significantly greater in participants who received semaglutide 2.4 mg than placebo. Changes in these values were generally similar in the two semaglutide-treated groups, although the data were not submitted to formal statistical analysis.

An important finding of STEP 2 was that individuals with type 2 diabetes can expect to lose approximately one-third less weight than those without this condition. This finding has been consistently observed with other weight loss medications,[40–42] as well as behavioral therapies.[43,44] The mechanisms responsible for diminished weight loss with type 2 diabetes are not well understood but may include reductions in energy expenditure, as well as in glycosuria, the latter which accompanies improved glycemic control.

STEP 3

This trial of 611 participants without diabetes was designed to maximize weight loss with semaglutide 2.4 mg by combining it with a more intensive program of behavioral therapy than used in STEP 1.[45] Thus, all participants (who were randomized to semaglutide 2.4 mg and placebo in a 2:1 ratio) received 30 visits with a registered dietitian over 68 weeks and were provided a 1000–1200 kcal/d meal replacement diet during the first 8 weeks. The intensive behavioral therapy (IBT) intervention succeeded at week 28 in inducing a mean loss of approximately 8% of baseline weight in placebo-treated participants, a loss that declined to 5.7% at week 68, most likely because of the decreased number of counseling visits during the second part of the intervention. Participants who received IBT combined with semaglutide 2.4 mg lost 16.0% of body weight at week 68 and achieved significantly greater improvements in multiple measures of cardiometabolic risk than the placebo-treated group.

Extrapolating across the results of STEP 1 and STEP 3, the addition of IBT appeared to increase the rate of weight loss with semaglutide during the first 12–16 weeks, but this combination was no more effective at week 68 than semaglutide combined with the less intensive (and less costly) diet and activity counseling provided in STEP 1. Further research is needed to determine the optimal frequency of lifestyle counseling required with semaglutide 2.4 mg. The medication's efficacy in improving self-reported appetite and in reducing objectively-measured energy intake may reduce the need for traditional behavioral counseling to support changes in these behaviors.

STEP 4

Following an average 10.6% reduction in baseline body weight achieved with semaglutide 2.4 mg during a 20-week run-in period, 803 adults without diabetes were randomly assigned (in a 2:1 ratio) to continued semaglutide or placebo.[46] Both groups received diet and activity counseling every 4 weeks as in STEP 1. Forty-eight weeks after randomization, participants assigned to remain on semaglutide lost an additional 7.1 kg, resulting in a net 17.4% reduction in baseline weight as measured from the start of the run-in. Placebo-treated participants, by contrast, gained 6.1 kg after randomization, resulting in only a net 5.0% loss from the start of the run-in. Weight regain in placebo-treated participants was associated with deterioration in improvements in cardiometabolic risk factors and quality of life, originally observed at the end of the run-in period.

The results of STEP 4 reveal that weight regain is likely when semaglutide is terminated, as it is when other anti-obesity medications or behavioral therapies are withdrawn. Further evidence is provided by Wilding et al, who examined

weight change 52 weeks after medication withdrawal in a subset of 327 participants from the STEP 1 trial.[47] Those originally treated by semaglutide regained 11.6 percentage points of their prior 17.3% reduction in baseline weight, while placebo-treated participants regained 1.9 percentage points of their prior 2.0% loss. These two studies suggest the possible benefits of long-term (indefinite) treatment with semaglutide (or other medications) to facilitate the maintenance of lost weight.

STEP 5

STEP 5 directly evaluated the duration of this medication's benefit in 304 adults without diabetes who were randomly assigned, in equal numbers, to 104 weeks of once-weekly semaglutide or matching placebo, both combined with lifestyle counseling (as provided in STEP 1).[48,49] At the end of trial, semaglutide-treated participants lost a mean 15.2% of baseline weight, compared with 2.6% for placebo. At week 52, participants in the two groups had mean losses of 15.6% and 3.0%, respectively, revealing that semaglutide-treated participants had excellent maintenance of weight loss from weeks 52 to 104. Moreover, the 104-week losses (for both groups) were within 0.5 percentage points of those observed at week 68 in STEP 1.

At week 104, significantly more semaglutide- than placebo-treated participants lost ≥5% of baseline weight (77.1 vs 34.4%), as well as ≥10% (61.8 vs 13.3%), ≥15% (52.1 vs 7.0%), and ≥20% of baseline weight (36.1 vs 2.3%). These categorical losses are similar to those observed in STEP 1, as are the greater improvements at week 104 in cardiometabolic risk factors in semaglutide- vs placebo-treated participants.

STEP 6

STEP 6 was a 68-week trial of 401 adults from east Asia, with or without type 2 diabetes, and a BMI of at least 27 kg/m^2 with two or more weight-related comorbidities or a BMI of 35 kg/m^2 or more with one or more weight-related comorbidity (one comorbidity had to be either hypertension, dyslipidemia, or, in Japan only, type 2 diabetes).[50] Participants were assigned (4:1:2:1) to once-weekly subcutaneous semaglutide 2.4 mg or matching placebo, or semaglutide 1.7 mg or matching placebo, plus lifestyle recommendations. The average decrease in body weight at week 68 was 13.2% in the semaglutide 2.4 mg group and 9.6% in the semaglutide 1.7 mg group versus 2.1% in the placebo group. At week 68, a larger proportion of participants in the semaglutide 2.4 mg and semaglutide 1.7 mg group than the placebo group had achieved a ≥5% (83 vs 72 vs 21%), ≥10% (61 vs 42 vs 5%), and ≥15% or higher reductions (41 vs 24 vs 3%) in baseline bodyweight. The 13.2% initial weight loss of patients treated with semaglutide 2.4 mg in this trial was slightly lower than the 14.9% weight loss in STEP 1, though STEP 1 did not include participants with type 2 diabetes who tend to have smaller weight losses.

STEP 8

Within the broader GLP-1RA medication class, differences exist in drug structure, efficacy, and adverse events. In this 68-week trial, 338 adults with overweight or obesity (without diabetes) were randomized 3:1:3:1 to once-weekly subcutaneous semaglutide 2.4 mg or matching placebo, or once-daily liraglutide 3.0 mg, or matching placebo, plus counseling for diet and physical activity.[51] This study focused on differences in efficacy and adverse event profiles between liraglutide and semaglutide. The mean body weight loss was 15.8% with semaglutide and 6.4% with liraglutide. At 68 weeks, the percent of participants in the semaglutide 2.4 mg group was higher than the liraglutide 3.0 mg group for achieving a ≥10% (70.9 vs 25.6%), ≥15% (55.6 vs 12.0%), and ≥20% weight loss (38.5 vs 6.0%). This study is one of the few head-to-head comparisons of individual therapies for weight management and demonstrated the superiority of semaglutide, relative to liraglutide, in weight loss. Many of the contraindications and adverse events of semaglutide are shared among other GLP-1RAs, including liraglutide; however, there are differences in occurrence and severity as further detailed below.

Candidates for Semaglutide

Selection of a particular anti-obesity medication depends on several factors including its efficacy, contraindications, potential adverse effects, and cost and the patient's comorbidities, insurance coverage, and preferences. Below we discuss

selection considerations for use of subcutaneous semaglutide for chronic weight management. There is an oral version of semaglutide that is approved by the FDA for type 2 diabetes, which was evaluated in 10 PIONEER phase 3 clinical trials.[52–61] The oral form of semaglutide is currently being tested for chronic weight management in the OASIS 1 study (NCT05035095) but is not yet approved for obesity treatment. Therefore, below we focus on data from the subcutaneous form of semaglutide.

Efficacy

The average weight loss efficacy of subcutaneous semaglutide 2.4 mg is high. However, some patients may be "non-responsive" to semaglutide, which using CMS guidelines is considered a <5% weight loss at 12 weeks. Data from STEP 1 showed that at 68 weeks, 7.6% of participants on treatment lost <5% of baseline weight, as did 26.8% of participants from STEP 2. General recommendations are that an anti-obesity medication should be stopped if a 5% or greater weight loss is not achieved after 12 weeks of a full-dose treatment. It is unclear if non-responders to one medication will be responders to a different agent.

Contraindications

Medullary Thyroid Carcinoma (MTC) and Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2)

Like other GLP-1RA medications, semaglutide has a boxed warning of a risk of thyroid c-cell tumors and is contra-indicated in people with a personal or family history of MTC or in patients with MEN 2. This warning is based on data from rodents demonstrating that semaglutide causes dose- and treatment duration-dependent thyroid C-cell tumors.[62] In rodents, thyroid C-cells highly express the GLP-1 receptor.[62] GLP-1 receptor agonists stimulate upregulation of the calcitonin gene expression, calcitonin release, C-cell hyperplasia, and increased risk of medullary adenomas and carcinomas in rodents.[62] However, these findings have not been found in nonhuman primates or in humans, which has been attributed to the very low thyroid C-cell density and GLP-1 receptor expression in thyroids of humans relative to rodents.[62,63] Serum calcitonin at concentrations ≥100 ng/L is highly specific as a tumor marker for neoplasia of the thyroid C-cells, with lower concentrations having lower specificity.[64] Among participants in the STEP 1 study, there was no significant difference between semaglutide and placebo-treated participants in change from baseline to 68 weeks in calcitonin levels.[21] In a meta-analysis of 11 trials, there was no increase in the risk of thyroid disorders in participants treated with semaglutide relative to placebo (RR = 0.75; 95% CI = 0.35, 1.57).[65] However, these events are rare, and people at individual or familial risk for MTC and MEN 2 and those with high baseline calcitonin were excluded from the STEP trials. In addition, most studies have been of relatively short duration. The rarity and long-term timeline of these events require larger-scale, longer-duration, randomized clinical trials designed to assess the effects of semaglutide on the thyroid system. Patients should be informed that it is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma in humans.

Hypersensitivity

A known hypersensitivity to semaglutide or any of its excipients is a contraindication for use of the medication. Caution also should be used in patients with a history of hypersensitivity to other GLP-1RAs. GLP-1RAs, including semaglutide, are protein-based molecules and are thus potentially immunogenic.[23,66] Antibodies can increase risk of local or systemic hypersensitivity. However, the clinical significance of anti-semaglutide antibodies appears to be low in most people. For example, in the STEP 6 trial, 2% of participants on semaglutide 2.4 mg developed anti-drug antibodies, and these were all cross-reactions with endogenous GLP-1 with no occurrences of anti-drug neutralized antibodies or anti-drug antibodies with endogenous GLP-1 neutralizing effects.[50] Rare but serious hypersensitivities including anaphylaxis and angioedema have been reported. Patients should seek medical treatment and discontinue the medication if they develop a serious hypersensitivity.

Pregnancy

Data from animal studies suggest that GLP-1RAs should not be used in pregnancy due to potential risks of embryofetal mortality, structural abnormalities, and alterations to growth.[61] There is insufficient human data to evaluate semaglutide

for use in pregnancy. Pregnancy is a contraindication for use of semaglutide, and semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Adverse Events

Patients prescribed semaglutide should be advised about potential side effects that may occur and provided guidance on how to mitigate these side effects.

Pancreatic Events

Acute pancreatitis and pancreatic cancer have been a concern of incretin-medications as a class.[67] No clear signal linking incretin-based therapies and acute pancreatitis or pancreatic cancer has been identified, though the FDA and EMA have indicated that pancreatitis should be considered a risk with incretin medications until further data are available. Asymptomatic, small, and dose-dependent increases in serum lipase and amylase have been reported with incretin-based therapies,[68] including semaglutide.[39,69] In STEP 1, mild acute pancreatitis occurred in 0.2% of semaglutide-treated participants compared to 0% of placebo-treated participants.[21] A longer cardiovascular outcome trial of semaglutide 1.0 mg for type 2 diabetes revealed no signals for pancreatic adverse events.[30] When combining all available cardio-vascular outcome trial data (including those from non-semaglutide GLP-1RAs medications) in a meta-analysis, a hazard ratio of 1.05 (95% CI = 0.78–1.41) was found for acute pancreatitis and 1.14 (95% CI = 0.77–1.70) for pancreatic carcinoma.[70] However, these are relatively rare complications, and the CVOTs and phase 3 studies were probably not sufficiently powered for their detection. The duration of the trials also may not have been long enough for patients to develop pancreatic cancer, especially considering it can take over 18 years for a normal duct cell to be initiated as a tumor cell and seed a parental clone from which pancreatic carcinoma can grow, and develop metastatic capacity, during which diagnosis typically occurs.[71] Since pancreatic adverse events are difficult to completely rule out, patients should be monitored for signs and symptoms of acute pancreatitis such as severe abdominal pain, with or without vomiting. The medication should be discontinued promptly if pancreatitis is suspected, and the patient should be referred for further evaluation and treatment. Semaglutide should not be restarted if pancreatitis is confirmed. This medication has not been assessed in patients with a history of pancreatitis.

Acute Gallbladder Disease

GLP-1RAs, as a class, are associated with a 28% increase risk for cholelithiasis.[72] In STEP 1, gallbladder-related disorders, most commonly cholelithiasis, were reported in 2.6% of participants in the semaglutide group and 1.2% of those in the placebo group.[21] Substantial and rapid weight loss can increase the risk of cholelithiasis and may be related to some instances of acute gallbladder disease, though it has also been suggested that changes in gallbladder motility that enhance biliary sludge formation and bile stones or a change in bile salts may be contributing mechanisms.[73] Patients should be advised about symptoms of gallbladder disease including right upper abdominal pain, jaundice, fever, or clay-colored stools. If suspected, gallbladder studies and clinical follow-up are indicated.

Gastrointestinal Adverse Reactions

Gastrointestinal side effects are common with semaglutide. In a pooled analysis from STEP trials 1–3, participants randomized to semaglutide 2.4 mg compared to those assigned to placebo reported more nausea (43.9 vs 16.1%), diarrhea (29.7 vs 15.9%), vomiting (24.5 vs 6.3%) and constipation (24.2 vs 11.1%).[74] These symptoms most commonly occurred during or shortly after dose titration and the median duration of constipation, nausea, diarrhea, and vomiting were 47, 8, 3, and 2 days, respectively. Most GI side effects were mild-to-moderate in severity (98.1%). Permanent discontinuation of medication due to GI side effects was reported by 4.3% of participants on semaglutide. Mediation analysis demonstrated that weight loss effects were unrelated to gastrointestinal side effects.[74]

Strategies to help mitigate gastrointestinal adverse events include delayed up-titration or re-titration. Maintaining patients on a lower tolerated dose, if effective, could also be used, as in the STEP 1 trial. Dietary modifications include reducing foods that cause symptoms (typically those that are high in fat), decreasing portion sizes, eating slowly, stopping when experiencing feelings of fullness, and avoiding eating late at night. Patients who were not able to tolerate

liraglutide due to gastrointestinal side effects may tolerate longer-acting semaglutide, though studies are needed to examine the effects of switching between agents.

Other Adverse Events

Several other adverse events have been reported with semaglutide.[75] For example, as with other GLP1-RAs, increases in heart rate averaging 2.5[39] to 5.4 beats per minute[51] have been observed in clinical trials. No increase in QT intervals or adverse cardiac events have been noted.[30,76] Heart rate should be monitored in participants taking semaglutide. In a weight loss maintenance trial with liraglutide 3.0 mg/day, the effect of the medication on increasing heart rate was attenuated when liraglutide was combined with a moderate-to-vigorous-intensity exercise program.[77] Encouraging moderate-to-vigorous-intensity exercise combined with semaglutide may help to mitigate increases in heart rate and improve cardiorespiratory fitness, but studies are needed to examine the efficacy of this strategy. The increase in heart rate with semaglutide is especially important to consider for patients with heart failure and other cardiac conditions, and the safety of semaglutide in this population is unclear. The effects of semaglutide in patients with obesity-related heart failure with preserved injection fraction are being examined in an ongoing clinical trial (STEP-HFpEF; NCT04788511).

Semaglutide should not be prescribed in patients with a history of suicidal attempts or active suicidal ideation. Patients should be monitored for depression, suicidal thoughts and behavior, and mood changes, and those who experience suicidal thoughts or behavior should discontinue semaglutide. Because semaglutide may delay gastric emptying, the absorption of oral medications may be delayed. Drug–drug interaction studies in healthy volunteers for subcutaneous semaglutide 1.0 mg did not show any clinically relevant changes in exposure to warfarin, digoxin, atorvastatin, or metformin.[78] Further studies are necessary to evaluate semaglutide 2.4 mg on medications with a narrow therapeutic index (eg, levothyroxine, warfarin), and patients taking any of these medications should be closely monitored.

This list of adverse events is not exhaustive. Adverse events are primarily derived from randomized clinical trials that occur under a wide variety of conditions and with different inclusion and exclusion criteria. Ongoing surveillance will be necessary to examine for additional and long-term adverse events.

Discontinuation Due to Side Effects

In STEP 1, discontinuation of study medication due to adverse events was reported in 7.0% of participants on semaglutide and 3.1% of participants on placebo. In pooled analyses of STEP trials 1–3, the most common adverse reactions leading to discontinuation in semaglutide versus placebo were gastrointestinal effects (4.3% in semaglutide vs 0.7% in placebo) with most discontinuations occurring in the dose-escalation period.[74] If patients do not tolerate a dose during dose escalation due to gastrointestinal side effects, delaying dose escalation for 4 weeks may help to mitigate symptoms.

Comorbidities

Obesity is a comorbidity to many conditions. In this section we highlight considerations for use of semaglutide 2.4 mg in patients with type 2 diabetes, cardiovascular disease, and chronic kidney disease. While weight loss is a central goal for obesity treatment, its benefit should be considered in the context of other treatment goals for these comorbidities.

Type 2 Diabetes

As shown in STEP 2, semaglutide at a higher dose of 2.4 mg produces larger weight losses than the 1.0 mg dose approved for type 2 diabetes.[39] Special considerations are needed when prescribing semaglutide in patients with type 2 diabetes. Semaglutide reduces blood glucose through stimulating glucose-dependent insulin secretion; thus, hypoglycemia is infrequent both in patients with and without type 2 diabetes.[21,39] In STEP 2, severe or blood glucose-confirmed symptomatic hypoglycemic episodes were reported in 5.7% patients randomized to semaglutide 2.4 mg, 5.5% of those randomized to semaglutide 1.0 mg, and 3.0% of individuals on placebo.[39] One severe hypoglycemic episode was reported during dose escalation with semaglutide 2.4 mg. The risk of hypoglycemia is low overall but increases when semaglutide is combined with diabetes medications known to cause hypoglycemia such as sulfonylureas, meglitinides and/or insulin therapy. Thus, doses of other diabetes medications may need to be lowered if initiating semaglutide, and

patients should be informed about hypoglycemia risk. For example, in STEP 2, patients taking sulfonylureas were instructed to reduce the dose by approximately 50% at treatment start, at the researcher's discretion.[39] Patients taking medications that carry the risk of hypoglycemia should be encouraged to monitor their blood glucose regularly and be provided education about preventing, recognizing, and managing hypoglycemia.

Diabetic retinopathy has been a concern with semaglutide, as well as other GLP-1 RAs.[79] In STEP 2, diabetic retinopathy was reported in 4.0% of patients receiving semaglutide 2.4 mg, 2.7% with semaglutide 1.0 mg, and 2.7% with placebo.[39] In the SUSTAIN 6 trial, which enrolled participants with type 2 diabetes, diabetic retinopathy complications occurred more frequently in the semaglutide than placebo group (3 vs 1.8%; HR = 1.76; 95% CI = 1.11, 2.78).[30] In pooled data from the SUSTAIN clinical trial program, participants who were at greatest risk for diabetic retinopathy had a longer duration of diabetes, higher HbA1c, were receiving insulin treatment, and had a history of diabetic retinopathy at baseline (83.5% among those with diabetic retinopathy versus 29.4% in the overall trial population).[80] Among participants with pre-existing diabetic retinopathy at baseline, the risk of diabetic retinopathy complications was increased in those treated with insulin. For semaglutide-treated participants without known pre-existing diabetic retinopathy at baseline, the risk of diabetic retinopathy was low and not statistically different than placebo.[80] Early worsening of pre-existing diabetic retinopathy was most evident in the initial 16 weeks, during which there was a rapid improvement in glycemic control. Caution should be taken when using semaglutide in patients with diabetic retinopathy, and retinal screenings should be performed regularly to detect progression of retinopathy. More gradual titration of semaglutide or down-titrating insulin could help mitigate rapid decreases in glucose concentrations and reduce the risk of diabetic retinopathy worsening, though further research is needed. A trial is ongoing to assess the long-term effects of semaglutide on diabetic retinopathy in patients with type 2 diabetes (FOCUS trial, NCT03811561). Semaglutide has not been studied in patients with type 1 diabetes.

Cardiovascular Disease

Despite the increase in heart rate seen with GLP-1RAs, these medications seem to improve cardiovascular disease through indirect effects on glucoregulatory systems, as well as through direct effects on cardiac function and attenuation of atherosclerosis.[81–83] The cardiovascular benefits of semaglutide were evaluated in the SUSTAIN 6 trial, a cardiovascular outcomes study conducted in 3297 participants with type 2 diabetes and established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), chronic kidney disease of stage 3 or higher, or an age of 60 years or more with at least one cardiovascular risk factor.[30] Participants randomized to semaglutide 0.5 mg or 1.0 mg, relative to placebo, had a reduced risk of major adverse cardiovascular outcomes (composite of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; 6.6 vs 8.9%; HR = 0.74; 95% CI = 0.58–0.95). These results were driven by a reduction in nonfatal stroke. It is unclear if these effects will translate to participants with obesity but without type 2 diabetes. The SELECT study (NCT03574597) is an ongoing randomized controlled trial to examine if semaglutide 2.4 mg subcutaneously once weekly is superior to placebo when added to standard of care for preventing major adverse cardiovascular events in people with established cardiovascular disease and overweight/obesity without type 2 diabetes.[84] As described above, the STEP-HFpEF will assess the effects of semaglutide in people with heart failure and obesity. Cardiovascular outcome studies of semaglutide to date have been carried out in high-risk populations to increase the hazard rate for major cardiovascular events, and such patients do appear to benefit from a reduction in adverse cardiovascular events. Little is known about cardiovascular benefits in lower-risk patients.

Renal Impairment

In exploratory analyses, semaglutide has demonstrated renoprotective effects.[85] These effects are most evident in patients with preexisting chronic kidney disease.[85] Semaglutide is not excreted by the kidneys, so dose reduction with impaired kidney function is not necessary. Rare cases of acute kidney injury have been reported in patients with chronic kidney disease stage 3b-4, and caution should be used in patients with later stage chronic kidney disease.[86] The FLOW study (NCT03819153) is currently ongoing and will prospectively assess the effects of semaglutide 1.0 mg on renal outcomes in people with type 2 diabetes and chronic kidney disease. Kidney function should be monitored in patients, especially

those with severe gastrointestinal adverse effects as these may result in dehydration. Dehydration should be prevented and treated to reduce risk of acute kidney injury.

Insurance Coverage/Cost

Anti-obesity medications are only used by 3% of eligible US adults.[87] A substantial barrier to the use of semaglutide, like other anti-obesity medications, is insurance coverage; 68% of payments for anti-obesity medications are out-of-pocket. Without coverage, the average wholesale price for a 30-day supply of semaglutide 2.4 mg is $1619 (USD).[88] This is similar to the cost of liraglutide ($1619) but higher than most other medications including orlistat (over the counter; $41), phentermine/topiramate ER ($223), and naltrexone/bupropion ER ($364). The cost-effectiveness of semaglutide is unclear, though one recent study demonstrated that semaglutide, relative to no treatment, diet and exercise alone, and other anti-obesity medications, was cost-effective at the willingness-to-pay threshold of $150,000 per quality-adjusted life year over a 30-year horizon.[89] As part of the shared decision-making process, insurance coverage and out-of-pocket expenses should be discussed openly with patients.

Patient Preferences

Patient preference is an important consideration in providing high-quality obesity treatment. Important attributes driving patient preferences for particular medications include dose frequency, efficacy, adverse event profiles, and if the medication is provided as an injection, injection preparation, type of device, and needle size.[90] Semaglutide is provided as a prefilled, single-dose pen with an integrated needle. While semaglutide has a reduced dosing frequency relative to all other obesity medications, it is a subcutaneous injection. Advances have been made in injection devices to reduce pain. However, the use of an injectable can be a barrier to initiation and adherence due to concerns about self-administering a medication, convenience, and social acceptance. Patients should be asked about barriers to adherence to giving a weekly injection. Obesity is a chronic disease and as shown in the STEP 1 extension study and STEP 4 trial, weight regain occurs with cessation of the medication. Thus, patients should be advised about the need for continued care for long-term weight loss.

Conclusions

Semaglutide is an effective medication for obesity treatment with average losses of 9.6–17.4% of initial body weight at week 68 and associated improvements in cardiometabolic and psychosocial indices. In addition to efficacy and safety, the appropriateness of prescribing semaglutide for an individual patient should consider contraindications, potential adverse effects, comorbidities and drug interactions, insurance coverage and cost, and patient preferences. New medications such as tirzepatide, a "twincretin" that combines GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonism, have shown weight losses of 20.9% of initial weight loss[91] and even greater weight losses than semaglutide.[92] Tirzepatide is being tested in the phase 3 SURMOUNT clinical trial program. Other dual medications such as CagriSema (2.4 mg semaglutide and 2.4 mg cagrilintide), a combined amylin/GLP-1 RA agent, have been tested in a Phase 2 study[93] and are currently being tested in the phase 3 REDEFINE clinical trial program (NCT05567796). There are several other weight loss medications in the pipeline. These novel medications will provide patients and providers with additional choices for effective weight management strategies. Studies and guidance will be needed to help providers and patients select an appropriate obesity treatment medication. Further studies are needed that provide longer term data on weight loss, safety, cardiovascular benefits of semaglutide and other anti-obesity medications, and their effects on morbidity and mortality. Additional studies also are needed that test head-to-head comparisons of weight loss medications. Further, a better understanding of the phenotypes of participants who may be well suited for specific medications and of the effects of switching medications among non-responders would enhance our understanding of best practices for patient selection and management.

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