Semaglutide for the treatment of obesity – a review

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Abstract

Increasing rates of obesity and its comorbidities continue to place a burden on individuals and health systems. Lifestyle interventions, although effective, are not always successful in long term management. The use of existing medicinal strategies, such as sibutramine and orlistat have not been very successful due to their own limitations. Semaglutide is a glucagon-like peptide-1 analogue that has been utilized in type 2 diabetes mellitus treatment. Its use in weight management has been recently explored in several studies. A review of literature can provide insight into whether semaglutide is a potential avenue for long term and sustainable weight loss. All studies reviewed identified that study participants on semaglutide experienced a significantly higher overall weight loss than placebo and most other comparison treatments. There were gastrointestinal adverse events recorded in most studies, but these did not seem to have an impact on the overall weight loss. Semaglutide provides a promising avenue for weight loss in obese and overweight individuals, although further research on management avenues for the GI events may ensure long term and sustained use.

Key words: semaglutide, obesity, weight loss

International rates of obesity have increased at an alarming rate in the last few decades. The World Health Organization (WHO) classifies an individual as overweight if they have a BMI of 25 or greater and as obese if their BMI is 30 or more (1). Between 1980 and 2013, prevalence of adults classified as overweight or obese increased by 27.5% (1). Comorbidities of obesity are numerous, with some of the most well-known including coronary heart disease, stroke, type 2 diabetes mellitus, and some cancers (2).

Treatment of obesity is best achieved through bariatric surgery, which is an invasive therapy for weight management (2). The leading non-invasive treatment is management of individual diet and behaviours (2). However, maintenance of weight loss using diet and behavioural changes is often challenging (3).

Medicinal strategies

Medicinal strategies for weight loss vary in modality and function. Sibutramine is a drug that has been shown to reduce bodyweight by inhibiting the reuptake of serotonin, noradrenaline, and some dopamine (4). This results in individuals reducing their food intake (4). The SCOUT trial conducted by James et al (2010) indicated a higher risk of cardiovascular events occurring in those who take sibutramine over a long period of time and who present with pre-existing cardiovascular conditions (5). Outcomes of this trial led to the suspension of the marketing authorisation for Sibutramine across Europe (6 and 7).

Orlistat is another medicinal strategy for weight loss, which works by reducing the digestion of triglycerides and reduces calorie absorption through faecal fat loss (4). However, long term persistence rates are very poor with high discontinuation rates (8).

Glucagon-like peptide-1 (GLP-1) is an incretin hormone responsible for nearly 70% of insulin secretion following the intake of food (9). For this reason, it was identified from the onset as an avenue of therapeutic interest in treating type 2 diabetes mellitus (9). However, its therapeutic use was limited due to its short half-life (9). The utilization of albumin binding increased its half-life and led to the development of liraglutide (taken once daily in type 2 diabetes mellitus and then semaglutide (taken once weekly), also for use in type 2 diabetes mellitus (9). Subsequently liraglutide obtained approval in Europe for use as an adjunct in weight management in obese patients and those with a BMI between 27-30 with weight related complications (10).

Recently, Semaglutide 2.4mg once weekly has gained approval in the USA as a treatment for obesity and in overweight patients with one associated weight related condition (11). A marketing authorisation from the European Medicines agency has also been sought by the manufacturers for approval of Semagltuide in management of obesity and overweight patients (12). The evidence for Semaglutide use in obesity is also under appraisal by the UK National Institute for Clinical Health and Excellence (NICE) (13).

Semaglutide mode of function

In order to understand the way semaglutide functions to reduce bodyweight, Blundell et al (2017) conducted a study (n=30) where they analyzed energy intake following dose-escalated subcutaneous injections of semaglutide. Participants were classified as obese (BMI of 30 to 45) and had not been diagnosed with type 1 or type 2 diabetes mellitus. There were two 12-week crossover treatment periods in this study and the treatment group was given escalating doses of semaglutide (0.25mg, 0.5mg, 1.0mg each for 4 weeks, ending with a last dose of 1.0mg at the end of the treatment period). Ad libitum energy intake was 35% lower in the semaglutide group compared to placebo, at lunch time. When observing all ad libitum meals and associated energy consumption, there was a 24% lower intake in the treatment group compared to placebo. Importantly, those who had been given semaglutide observed a mean body weight loss of 5kg compared to an increase by 1kg in the placebo group (14).

The authors also analyzed food preference using the Leeds Food Preference Task (LFPT), which can measure aspects of food preference and rewards. Results indicated that those in the semaglutide group had a reduced explicit liking for foods that were non-sweet and also high-fat (14). This study gives informed insight into the mechanism by which semaglutide functions, with an effect on energy intake leading to overall weight loss (14).

Semaglutide compared to liraglutide

While semaglutide is administered once weekly, its predecessor liraglutide is taken on a daily basis (9). A comparison of the two GLP-1 analogues in weight loss is useful in identifying the best modality. O'Neil et al (2018) conducted a study comparing the two which took place across 71 clinical sites situated in 8 different countries. Trial participants (n=957) were given varying doses of liraglutide, semaglutide, or placebo. All participants had a BMI of 30 or more and did not present with diabetes. Although liraglutide and semaglutide are both analogues of Glucagon-like peptide-1 (GLP-1), semaglutide is longer-acting. Following 52 weeks of treatment, results indicated a significant difference in weight loss when comparing the two treatment groups with placebo. There was also a significant difference in weight loss between semaglutide and liraglutide groups, with an increased weight loss observed at week 52 for those on doses of 0.1mg semaglutide or higher compared to participants given 3.0mg of liraglutide. While there was a higher reporting of gastrointestinal adverse events amongst treatment groups, 97% of these were classified as either mild or moderate (15).

Semaglutide and lifestyle changes

Studies have also been conducted where additional behavioural therapy has been added into the treatment regimen. The STEP 3 study by Wadden et al (2021) was carried out across 41 sites over 68 weeks (n=611) (16). Subjects were either overweight or obese and had not been diagnosed with type 2 diabetes mellitus. The treatment group was given 2.4mg semaglutide weekly in addition to a low-calorie diet for the initial 8 weeks, and intensive behavioural therapy throughout the length of the trial. The placebo group had the same, with the absence of semaglutide. The mean body weight change in the treatment group was -16.0%, compared to a change of -5.7% for the placebo. In the treatment group, 86.6% of participants lost 5% or more of their bodyweight, compared to 47.6% of the placebo achieving the same result (16).

Another trial by Khoo et al (20210 (n=1961) included participants who had a BMI of 30 or greater (or 27 or greater if presenting with weight related comorbidities) and were not diagnosed with type 2 diabetes mellitus (17). Treatment group was given 2.4 mg of semaglutide subcutaneously once a week for 68 weeks, and also had a lifestyle intervention of counselling sessions every 4 weeks. These sessions were to provide guidance to participants so that they were able to reduce caloric intake by approximately 500kcal per day and increase physical activity to approximately 150 minutes per week. There was a significant difference in change in body weight when comparing placebo and treatment groups. By week 68, participants in the semaglutide group presented with a mean change in body weight of -14.9% versus -2.4% in the placebo group. For one third of subjects in the treatment group, their weight loss of at least 20% of baseline weight was comparable to results of post sleeve gastrectomy (a form of bariatric surgery which yields 20-30% weight loss 1-3 years post-surgery) (17).

Sustainability

Long-term adherence to any intervention is important in sustaining weight loss and achieving resulting health benefits. In the STEP 4 study, Rubino et al (2021) enrolled 902 participants across 73 sites to see how they fared in receiving long-term (48 weeks) semaglutide versus placebo following an initial 20 week run of 2.4mg of semaglutide weekly (18). In addition, all participants were provided with monthly counselling, where they were guided and reviewed to reduce caloric intake by 500kcal per day and increase physical activity to 150 mins per week. Subjects did not have diabetes mellitus and had a BMI of 30 or more or 27 or more if they had an existing weight-related comorbidity. Following the initial 20 week period where all participants were given weekly semaglutide, there was a reduction in mean body weight of 10.6%. By the end of 68 weeks, those who had continued semaglutide saw a mean body weight reduction of 7.9% compared to an increase in body weight by 6.9% in the group that was switched to placebo from semaglutide. Significantly, 39.6% of participants who continued on with semaglutide lost 20% or more of their body weight compared to 4.8% in the placebo group. 71.4% of participants registered gastrointestinal tract disorders as adverse events, although most were not very severe. This study indicates long term and sustainable weight loss is possible with ongoing use of semaglutide (18).

Risks of Semaglutide

An important caveat in the studies reviewed is the higher incidence of gastrointestinal issues in those in the treatment group. In some cases (such as in the STEP 3 trial) this led to a higher percentage of participants discontinuing the treatment (3.4% vs 0% in the placebo) (16). Lingvay et al (2020) conducted a mediation analysis to identify whether individuals who experienced gastrointestinal (GI) issues when on semaglutide had any difference in weight loss (19). This study included patients who said “yes” to vomiting, nausea or any adverse GI event in three previously carried out studies which looked at the effects of semaglutide on weight loss versus other treatments. Although weight loss has been shown to be greater in patients who experience GI side effects from GLP-1 agonists, this study indicated that semaglutide demonstrates greater weight loss independent of its higher incidence of side effects. Because side effects may impact adherence to drug protocol, further inquiry into GI side effect management may be warranted.

Conclusion

Semaglutide has shown to be a promising avenue for weight loss in obese and overweight individuals. Approval has been granted for its use in weight management by the Food and Drugs Administration (FDA) and is currently being reviewed by UK National Institute for Clinical Health and Excellence (NICE). In order to ensure sustained and continued use, further research into the management of GI adverse events may be useful. Long term use resulting in sustained weight loss could help reduce the burden of obesity and its related comorbidities.

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