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GLP-1 Receptor Agonists:
Semaglutide (Wegovy) and Liraglutide (Saxenda)

Introduction

Obesity is a chronic, relapsing disease that places a substantial health burden in affected individuals. This is especially true for those with chronic pain due to the production of inflammatory chemicals by fat cells that contribute significantly to chronic pain. So, excessive fat is not just a mechanical burden contributing to chronic pain but also a chemical burden that drives inflammation and pain.

Guidelines for weight loss and treating obesity encourage lifestyle modifications, including decreased caloric intake, moderate to vigorous exercise, and behavioral therapy as the first steps in the intervention. Achieving and maintaining long-term weight loss is very challenging for many reasons, but largely because of the difficulty of adhering to the necessary lifestyle interventions of diet and exercise.

To gain substantial clinical benefits from weight loss, including reducing cardiovascular risks and pain, it is generally necessary to sustain a weight loss of 5% to 15% of one's total body weight.

Weight Loss Medications

There are currently four FDA-approved medications on the market for weight loss, namely phentermine-topiramate (Qsymia), orlistat (Xenical), naltrexone-bupropion (Contrave), and the glucagon-like peptide-1 receptor agonists (GLP-1 RA) liraglutide (Saxenda) and Wegovy (semaglutide). Lorcaserin (Belviq) was previously given FDA approval but was recalled at the beginning of 2020 due to an associated increased risk of malignancies.

However, most anti-obesity medications provide only moderate effectiveness (3%-8% body weight reduction beyond lifestyle interventions alone). Short-term treatment (3-6 months) generally fails to produce either persistent weight loss or long-term health benefits. Several agents also have safety concerns. New treatments that are well-tolerated and able to produce substantial, sustained weight loss over the long term, are needed.

GLP-1 Receptor Agonists

A new class of medications appears to meet these needs, glucagon-like peptide 1 (GLP-1) receptor agonists.

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Weight loss with GLP-1 receptor agonists is thought to be due to improved appetite control with subsequent reduced food intake. They are also successful at improving glycemic control by stimulating insulin secretion and inhibiting glucagon secretion without precipitating hypoglycemia. There are currently two FDA approved GLP-1 receptor agonists: Semaglutide (Welgovy) and Liraglutide (Saxenda).

Semaglutide (Welgovy)

Subcutaneous semaglutide (Welgovy), a GLP-1 receptor agonist, has shown promise for glycemic control as well as for promoting weight loss in patients both with or without type 2 diabetes. Recent studies using once-weekly 2.4 mg doses of subcutaneous semaglutide for the treatment of overweight/obesity suggest it to be safe and effective.

A recent multi-center, randomized clinical trial published in 2021 evaluated overweight/obese adults who maintained once-weekly treatment for up to 68 weeks with subcutaneous semaglutide. The study subjects experienced sustained weight loss along with significant improvements in waist circumference, systolic blood pressure, and physical functioning.

Weight loss achieved during the study period reached a plateau at week 60 to 68, ultimately resulting in an estimated reduction of 17.4% body weight over the trial. Notably, 86% of participants attained at least 5% weight loss. In contrast, participants who switched back to placebo after 20 weeks gradually regained weight.

Maintenance of Treatment

Similar to trials of other anti-obesity medications that emphasize the chronicity of obesity, this study identified the need for continuous, prolonged weekly treatment with semaglutide in order to maintain maximal weight loss. It is not recommended as a short term treatment for rapid weight loss.

The significant and sustained weight loss demonstrated with continued semaglutide in this study was also accompanied by improvement in waist circumference, lipid profiles, and glucose metabolism, all of which are significant cardiovascular risk factors. Sustained weight loss of this magnitude has been shown to improve obesity-related complications including type 2 diabetes.

In patients with diabetes type 2 at high risk of cardiovascular disease, semaglutide not only has demonstrated improvement in diabetes and body weight but also it has also been shown to lower the rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The superiority of semaglutide in reducing body weight compared with other anti-diabetic medications has been relatively well established by clinical trials.

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Dosing of Semaglutide

Semaglutide, administered with a prefilled pen injector, is initiated at a dose of 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks until reaching the maintenance dose of 2.4 mg weekly by week 16. In the presence of unacceptable side effects with the 2.4-mg dose, lower maintenance doses are recommended. The half-life of semaglutide extends to 160 hours, supporting once-weekly administration.

Individual counseling sessions are recommended every 4 weeks to help patients adhere to a reduced-calorie diet (500-kcal deficit per day) and increased physical activity (with 150 minutes per week of physical activity, such as walking, is encouraged). Both diet and activity may be recorded daily in a diary or by use of a smartphone application or other tools and to be reviewed during counseling sessions.

Adverse Effects

Typically with the class of GLP-1 receptor agonists the most frequently reported adverse events are transient and mild to moderate in severity and gastrointestinal in nature (namely nausea and vomiting, constipation and abdominal pain). These events occur mostly during the run-in period, when semaglutide is escalated to the target dose. Over the entire trial period, few participants discontinued treatment (5.3%) because of adverse events and those who continued treatment beyond 20 weeks were unlikely to experience significant problems thereafter.

Safety

Essential differences in safety between the weight loss medications should also be considered. As pointed above, semaglutide, like other GLP-1 receptor agonists, is associated with GI adverse effects, namely nausea and vomiting. More serious adverse effects include pancreatitis and medullary thyroid carcinoma, although thyroid cancers have not been reported in humans. Treatment with GLP-1 RAs is contraindicated in patients with a history of chronic or idiopathic acute pancreatitis. Other contraindications include a family or personal history of multiple endocrine neoplasia type 2, impaired renal function, or medullary thyroid cancer. These restrictions are based on findings from animal studies.

A higher incidence of retinopathy complications, including vitreous hemorrhage and blindness, was reported in patients treated with semaglutide compared with placebo.This was considered to be related to the rapidity and magnitude of glycemic improvement rather than a direct side effect of semaglutide.

Gall bladder-related issues, principally gall stones, ranged between 0.2% and 4.9%. Cardiovascular issues, including tachycardia and arrhythmias, ranged between 1.5% and 9.8% in STEP trials 1–4.

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Phentermine-topiramate has been associated with severe cardiovascular outcomes, while orlistat intake increased the risk of renal failure and hepatotoxicity. Semaglutide, on the other hand, lowered death from cardiovascular causes by 26% when compared with placebo. Semaglutide does not affect overall renal function and is considered safe for use in patients with moderate renal impairment. Based on these safety findings, semaglutide might be a better alternative to the anti-obesity medications currently on the market. It should also be noted that, semaglutide (like other GLP-1 analogs) has a low risk of hypoglycemia.

Liraglutide (Saxenda)

Another GLP-1 receptor agonist, liraglutide, is also approved for weight management at a 3.0-mg/day dosage. A 56 week study with liraglutide demonstrated weight losses of 10% body weight in 33% of subjects and 15% body weight of subjects in 14% of subjects. in clinical trials, weight loss with liraglutide was of lesser magnitude and appeared to plateau earlier (at 20 or 40 weeks) compared with semaglutide (palteaing at 60-68 weeks).

A 2022 systematic review of the effects of semaglutide and liraglutide in individuals with obesity or overweight without diabetes concluded that liraglutide and semaglutide therapy both led to clinically relevant (⩾5%) weight loss in 48.2%–88.7% of obese/overweight adults without diabetes. Furthermore, both liraglutide and semaglutide were well-tolerated.

Liraglutide is structurally highly similar to semaglutide with only a few chemical modifications. The once-daily dosing regimen of 3.0 mg liraglutide has been approved by the FDA for the treatment of obesity. However, the once-daily injection regimen can cause physical and financial stress for some adults, so the once-weekly injection model for the GLP-1RAs has been implemented by some.

One study directly compared liraglutide and semaglutide and concluded that semaglutide 0.2mg *once-daily* showed superior weight loss than liraglutide 3.0 mg once-daily. Other studies also found that semaglutide was more effective in reducing body weight than liraglutide; however, the vast majority of the studies were based on patients with diabetes, with weight loss not being the main primary outcome.

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Conclusion

Based on the effectiveness of these FDA approved GLP-1 receptor agonists, they may offer pharmacological options for overweight and particularly obese patients who might be considering bariatric surgery, which is currently considered the most effective and reliable intervention available for weight management. In comparism, 40% of participants in the semaglutide study trial who took semaglutide for 68 weeks lost 20% or more of their body weight, which approached the level of weight loss seen with sleeve gastrectomy.

It remains important to combine lifestyle modifications such as dietary and physical activity in the treatment of obesity. Dietary modification is fundamental for the long-term management of obesity and includes a variety of dietary interventions, including intermittent fasting, calorie restriction and different macronutrient compositions (e.g. low-fat diets, low-carbohydrates), avoidance of special foods, and following a certain dietary pattern (e.g. Mediterranean diet).

Physical activity is also crucial for successful weight loss, as it can induce energy deficit and preserve lean muscle mass. The American College of Sports Medicine (ACSM) recommends that individuals exercise 150–250 minutes/week, > 150–250 minutes/ week, and 200–300 minutes/week to prevent weight gain, achieve weight loss, and maintain weight loss, respectively. Another clinical trial showed that exercise combined with liraglutide was approximately twice as effective as either treatment alone in reducing body weight and body-fat percentage. It was also associated with the improvements in insulin sensitivity, cardiorespiratory fitness, and maintaining a good mood.

The optimal treatment for obesity should be individualized where treatment decisions consider age, coexisting diseases, drug tolerance, and economic and local medical conditions, For example, naltrexone/ bupropion should not be The ideal treatment for obesity should be a highly individualized, personalized medicine. Treatment decisions will consider age, coexisting diseases, drug tolerance, and economic and local medical conditions. For example, naltrexone/ bupropion does not apply to uncontrolled hypertension patients and phentermine/topiramate treated patients should be monitored closely for depression. However, there is no consensus or guidelines to help clinicians make decisions on which drugs to choose.

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