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Long-Term Management of Obesity with Once-Weekly Semaglutide: Efficacy and Safety in Clinical Trials

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Short commentary

Over 800 million people globally are categorized as obese, defined as having a Body Mass Index (BMI) of 30 or more. About 42% of adults in the US suffer from obesity [1], and the yearly cost of obesity-related medical costs is projected to be $173 billion. Given that obesity is a chronic, relapsing illness that affects many people, long-term care is required. Health care costs, morbidity, and death are all significantly impacted by obesity. Its clinical ramifications affect almost all organ systems.

The mainstay of treatment for those who are overweight or obese is changing their lifestyle, which typically only produces a small weight loss that is often regained. Furthermore, it is hard to maintain this weight loss due to metabolic adaptation, which promotes a gradual recovery of body weight. Pharmacotherapy is recommended for people with a BMI of 30 or higher (or 27 or higher with coexisting conditions), but the current medications have limitations in terms of efficacy, safety, and cost. Until recently, the only significant weight loss that could be achieved with medication was through lifestyle intervention. Pharmaceutical interventions for obesity are a useful complement to lifestyle modifications. Semaglutide has demonstrated effectiveness in promoting weight loss; it was formerly licensed for the treatment of type 2 diabetes and the reduction of cardiovascular risks [2].

Semaglutide is a once-weekly GLP-1 RA with documented effects on blood pressure, weight, and glucose levels. The Food and Drug Administration (FDA) approved semaglutide as an antidiabetic medicine on December 5, 2017, and the European Medicines Agency (EMA) approved it on February 8, 2018 [4]. It is thought that semaglutide reduces hunger and, as a result, lowers energy intake through actions in the hypothalamus and region postrema of the brain.

The first research known as STEP 1 trial, assessed the safety and effectiveness of semaglutide, an analogue of glucagon-like peptide-1 (GLP-1), given subcutaneously to people who were overweight or obese once a week at a dose of 2.4 mg. Included were 1961 individuals with a BMI of 30 or above (or 27 or higher with weight-related disorders), omitting those with diabetes, pancreatitis, history of obesity surgery, or current use of antiobesity medications. In individuals who were overweight or obese, GLP-1 improved cardiometabolic risk factors and dramatically decreased body weight [3]. This enhances its possible application as a successful obesity treatment. The same dosage of semiglutide was found to significantly lower BMI and enhance cardiometabolic risk factors in obese adolescents in another trial.

In STEP 2 trial, weight management in persons with type 2 diabetes and overweight or obesity was compared to the safety and effectiveness of a once-weekly subcutaneous semaglutide 2.4 mg versus semaglutide 1.0 mg (the dose authorized for diabetes treatment) and placebo. 210 participants were included in the intention-to-treat analysis and randomly assigned to receive semaglutide 2.4 mg (n=404), semaglutide 1.0 mg (n=403), or placebo (n=403). More patients who were on semaglutide 2.4 mg than those who were on placebo lost at least 5% of their body weight. In conclusion, semaglutide 2.4 mg once a week produced a better and clinically significant reduction in body-

weight compared to placebo in people with type 2 diabetes and overweight or obesity [4].

In STEP 3 trial, researchers evaluated the effects of once-weekly subcutaneous semaglutide (2.4 mg) against a placebo in people with overweight or obesity who did not have diabetes. This was done over a 68-week period as an adjuvant to intensive behavioral therapy and an initial low-calorie diet. After 68 weeks, those receiving semaglutide treatment lost considerably more weight than those receiving a placebo in a study involving 611 people. The mean weight loss in the semaglutide group was -16.0%, while the placebo group's weight loss was -5.7%. Compared to the placebo group, a higher number of semaglutide users lost at least 5%, 10%, and 15% of their body weight. therefore In people with overweight or obesity, once-weekly subcutaneous semaglutide, combined with rigorous behavioral therapy and an initial low-calorie diet, resulted in considerable weight loss over a 68-week period [5].

In STEP 4 trial, a comparison was made between maintaining with once-weekly subcutaneous semaglutide medication (2.4 mg) versus switching to a placebo to maintain weight in people who are overweight or obese following a 20-week semaglutide run-in period. Compared to those who switched to a placebo, those who stayed on semaglutide saw significant improvements in their physical functioning, decreased blood pressure, decreased waist circumference, and weight loss. When compared to switching to a placebo, semaglutide 2.4 mg once weekly resulted in maintained weight loss over 48 weeks [6].

The STEP 5 trial evaluated the long-term treatment of people with obesity or overweight with at least one weight-related comorbidity who were not diabetics. It compared the safety and efficacy of once-weekly subcutaneous semaglutide 2.4 mg vs placebo (both plus behavioral intervention). The achievement of a weight loss of ≥5% at week 104 and the percentage change in body weight were the co-primary objectives. Following week 104, a greater number of individuals in the semaglutide group than in the placebo group had lost ≥5% of their starting weight. In summary, semaglutide treatment resulted in significant, long-lasting weight loss over 104 weeks compared to placebo in people who were overweight (with at least one weight-related condition) or obese [6].

Within STEP 6 and 7 trial, When given semaglutide 2.4 mg once a week, obese adults from East Asia with or without type 2 diabetes saw better and clinically significant weight losses as well as larger reductions in their visceral abdominal fat area when compared to placebo. This suggests that semaglutide is a promising treatment option for managing weight in this population. When combined with dietary and exercise coaching, in STEP 8 trial participants who were overweight or obese but did not have diabetes saw significantly more weight loss at 68 weeks when given subcutaneous semaglutide once a week as opposed to once a day [7]. (The STEP 9 experiment is now underway, which is helping to improve obesity as a chronic condition. It assesses the effects of semaglutide 2.4 mg once weekly on individuals who have osteoarthritis in their knees and are obese. The gastrointestinal system like nausea and dirrehea were the specific adverse event that was observed in every trial. Most patients experiencing adverse events their symptoms were classified into mild to moderate category, their symptoms were promptly resolved. The prevalence and financial cost of obesity are highlighted in the article. Modest and unsustainable weight loss is a common result of traditional therapy approaches including lifestyle modifications. Treatment of obesity may benefit greatly from the once-weekly GLP-1 receptor agonist semaglutide. Research has shown through clinical trials, such the STEP investigations, that semaglutide improves cardiometabolic risk factors and dramatically lowers body weight in obese adults and adolescents. Semaglutide offers a viable and sensible long-term therapeutic option for treating obesity, resulting in significant and sustained weight loss, despite certain gastrointestinal side effects.

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