Liraglutide versus Semaglutide: Long Term Weight Loss Management in Obese Individuals

by

McKenzie Burke, PA-S

Bachelor of Exercise Science, North Dakota State University, 2018

Contributing Authors:

Julie Solberg, PA-C

Russell Kauffman, MPAS, PA-C

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfilment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2023

Table of Contents

Acknowledgments

I would like to thank my scholarly project advisor, Professor Julie Solberg as well as Professor Russell Kauffman, for their assistance and guidance with this project. I would also like to thank Dr. Marilyn Klug who assisted and offered her expertise with data analysis on this project. I would also like to extend my gratitude and appreciation to Dr. Brent Hella from Fargo's Valley Weight Loss Clinic and to Dr. Keena Byrd-Moro, DNP from Monument Health in Spearfish, SD for speaking with me and providing their expertise in regard to my topic and offering guidance based on their standard clinical practice and application with the use of the pharmaceuticals discussed throughout this project. Lastly, I would like to thank my family, friends, and my UND PA student colleagues for their unwavering support and patience throughout the entirety of PA school.

Abstract

Obesity has been a source of complications affecting multiple aspects from a physiological and psychological standpoint which has been steadily growing. There are a multitude of weight loss programs and medications with the idea of sustaining consistent weight loss to include use of the pharmaceuticals discussed within this review. The purpose of this literature review is to compare the efficacy and safety with use of liraglutide versus semaglutide (GLP-1 receptor agonists) in respect to long term weight loss management while in conjunction to lifestyle modifications within the obese population. Thorough research has been done with the aid of health science databases to include PubMed, ClinicalKey, and EBSCO. All of the studies were published between the year 2014 to 2022 and utilized human subjects greater than or equal to 18 years of age with specificity to subjects who were classified as "obese" based on their body mass index (BMI). The studies which were used throughout this review were composed of randomized control studies and systematic reviews. The data presented shows that both pharmaceuticals represented significant weight loss compared to their corresponding placebo, however concrete evidence was discovered that semaglutide was noted to be superior compared to liraglutide in the form of weight loss management in obese individuals. Furthermore, the current research that is available and studied does not conclusively provide enough evidence nor has been studied properly when considering long term use of these pharmaceuticals.

Keywords: GLP-1 receptor agonist; liraglutide; semaglutide; safety; efficacy; adverse events; lifestyle modifications; obesity; weight loss; long-term management

Introduction

Obesity can be defined as an abnormal or excessive accumulation of fat presenting as a risk to an individual's health in many ways. The obesity epidemic is termed as a global and multifactorial disease resulting from a combination of genetic and environmental factors in association to several comorbid complications to include cardiovascular diseases, metabolic syndrome, type 2 diabetes mellitus, cancer, and many more. The use of body mass index (BMI) calculations utilizes weight-for-height which is defined as a person's weight in kilograms divided by the square of their height in meters to classify individuals as underweight, normal, overweight obese, or morbidly obese. The number of overweight and obese individuals have increased substantially, nearly tripling since 1975. As defined by the World Health Organization in 2016, approximately 1.9 billion adults, who are 18 years or older, were deemed as overweight and 650 million adults were deemed as obese (Shah, et al. 2014). In regard to losing weight and weight loss management there are a multitude of options on the pharmaceutical market to be utilized. However, attaining healthy weight loss is not about a specific "diet or program", but a lifestyle alteration.

To achieve successful maintenance of weight loss, the World Health Organization and US Academy of Nutrition and Dietetics recommend lifestyle modifications to include reducing excessive energy intake and improving dietary quality. However, the use of adjuvant pharmacotherapy, to include the pharmaceuticals to be discussed, have been found to be successful with some individuals' weight loss journey. The use of pharmacotherapy such as

glucagon-like peptide 1 (GLP-1) receptor agonists have primarily been promoted to aid with the diabetes epidemic and insulin resistance. Yet, has been utilized as a weight loss agent in recent years from known pathophysiology secondary to the mechanism of action promoted within the gastrointestinal tract with delay of gastric emptying and direct regulation of appetite. Several studies that investigated the mechanism of action of GLP-1 receptor agonists found evidence that GLP-1 receptors are located in the hypothalamus which is involved with the regulation of food intake. Acute administration of these agents resulted in reduced feelings of hunger secondary to an increase in functional connectivity of the nucleus tract thus reducing energy intake and facilitating weight loss (Ard, et al. 2021).

Statement of the Problem

The prevalence of obesity continues to increase despite the use of several approved anti-obesity medications secondary to a multitude of factors to include lack of proper therapy, poor uptake and usage of therapy, adverse effects, and poor compliance. This has been characterized as a rising epidemic with no specific cure to the disease associated with high rates of relapse. Nonetheless, the search for manageable and successful treatments continues. Research has further proven the effects of pharmaceutical agents in conjunction to lifestyle modifications and weight management, but long-term use is in question. Specifically, the safety and efficacy of use with liraglutide versus semaglutide, both primarily labeled as diabetic treatment agents, but have been found to be successful, off-label weight loss agents in the acute setting. With long term use of GLP-1 receptor agonists, the question of effectiveness and safety plays a significant role along with consistent and healthy weight loss while in conjunction to lifestyle modifications of dietary changes and induction of exercise.

Research Question

In comparing GLP-1 receptor gonist pharmaceuticals, liraglutide vs. semaglutide, what is the efficacy and safety of use for obese individuals with a BMI (Body Mass Index) greater than or equal to 30 kg/m2 in long term weight management in conjunction with lifestyle modifications?

Research Methods

A literature review was performed using electronic search databases, PubMed and Clinical Key. Keywords and mesh terms were utilized to define a multitude of literature discussing the use of GLP-1 receptor agonists, liraglutide and semaglutide, in regard to weight loss. Further search was performed to analyze specifically the efficacy and safety of these pharmaceuticals in obese individuals. In total, approximately 927 studies for semaglutide and weight loss were revealed, 2,498 studies for liraglutide and weight loss, and 692 studies for comparison of semaglutide and liraglutide. Primarily clinical trials were utilized throughout this project. Several studies were excluded as most of the search results consisted of narrative reviews from other trials. Studies that included specific populations such as specific age groups and studies solely analyzing individuals with type 2 diabetes mellitus were excluded. All studies that were not in English were excluded. Studies that included solely analyzed cardiovascular, endocrine, or gastrointestinal interventions in combination with the GLP-1 receptor agonists were excluded. Overall, 12 studies met the final criteria for this review.

Literature Review

Overview of Liraglutide in the use of weight management

Pi-Sunyer, et al. (2015) conducted a 56-week, randomized, placebo-controlled, double-blind trial that was aimed to evaluate the use of 3.0 mg once-daily subcutaneous injection of liraglutide in conjunction to a reduced calorie diet and increased physical activity for weight management in overweight or obese adults (greater than or equal to 18 years of age) who do not have type-2 diabetes at baseline. This study was conducted at 191 sites in 27 countries which involved 3,731 patients with a baseline body-mass index (BMI) greater than or equal to 30 kg/m2 or those who had a BMI greater than or equal to 27 kg/m2 with untreated or treated dyslipidemia or hypertension. Eligible patients were randomly assigned in a 2:1 ratio to receive once-daily subcutaneous injections of Liraglutide or placebo. Doses were initially started at 0.6 mg with weekly dosage increase in 0.6 mg increments to the goal dose result of 3.0 mg. Both the treatment and placebo groups received monthly standardized counseling on lifestyle modifications. Patients were evaluated every 2 weeks until week 8, patients were then further evaluated every 4 weeks until week 44, and then were again further evaluated every 2 weeks until the end of trial. After the 56-week period, patients who were in the treatment group and received Liraglutide were randomly assigned in a 1:1 ratio to continue receiving Liraglutide or switch to the placebo group for an additional 12 weeks to assess where efficacy was maintained after discontinuation of Liraglutide treatment.

Three coprimary endpoints were assessed at the end of trial which included weight change from baseline, proportion who lost at least 5% of bodyweight from baseline, and proportion of those who lost more than 10% of their bodyweight from baseline. Secondary end points included BMI changes from baseline, waist circumference (cm), glycemic control variables (glycated hemoglobin, fasting glucose, fasting insulin, fasting C-peptide),

cardiometabolic biomarkers (vital signs, fasting lipid profile), and health-related quality of life which was assessed using Medical Outcomes Study 36-Item Short-Form Health Survey, Impact of Weight on Quality of Life-Lite, and Treatment Related Impact Measure-Weight questionnaires. After the initial 56 weeks, 71.9% (N=2437) of patients completed the trial in the liraglutide group and lost a mean of 6.7-8.0% of their body weight (7.3-8.4 kg). Compared to, 64.6% (N=1225) of patients completed the trial in the placebo group and had lost a mean of 2.6-5.7% of their body weight (2.8-6.5kg). Liraglutide was shown to be superior compared to the placebo in respect to all three coprimary end points noted above. A total of 63.2% of patients in the Liraglutide group compared to 27.1% in the placebo group lost at least 5% of their body weight from baseline ($p<0.001$), and 33.1% and 10.6% lost more than 10% of their body weight from baseline ($p<0.001$). Liraglutide administration had shown reductions in cardiometabolic risk factors to include waist circumference, blood pressure, improved glycemic control, and inflammatory markers. Strengths of this trial include a large sample size, independent blinded adjunction of specific adverse events, and a lifestyle intervention with resultant weight loss. Limitations of this trial include short duration of trial in relation to long term efficacy and safety, both the treatment and placebo group were predominantly white, exclusion of individuals with Type-2 diabetes to participate in the trial, and no correction for multiple testing was performed for the secondary endpoints (Pi-Sunyer, et al. 2015). The trial was sponsored by Novo Nordisk who also planned and performed the statistical analyses, provided editorial and writing assistance, as well as provided the trial drugs which may present as a potential bias.

In conclusion, 3.0 mg of once-daily subcutaneous injection of Liraglutide in adjunction with lifestyle modifications was shown to increase weight loss in overweight or obese patients as well as shown improvements in health-related quality of life. (Pi-Sunyer, et al. 2015)

A 56-week, randomized, double-blind, placebo controlled, multicenter trial was completed at 17 sites throughout the United States by Wadden, et al. (2020) that was center focused around the effect of GLP-1 receptor agonist, liraglutide, in addition to intensive behavioral therapy (IBT) in regard to weight loss and management in obese adults (greater than or equal to 18 years of age). Those who were analyzed were screened with a basal metabolic index (BMI) greater than or equal to 30 kg/m2. As a secondary objective, this study investigated the effects of the interventions mentioned above on cardiometabolic and other efficacy end points, along with evaluating the safety and tolerability of liraglutide 3.0 mg vs. placebo in conjunction to IBT. The sample size included 282 participants in total with a 1:1 randomization. Key exclusion criteria were evaluated during the screening process to include a hemoglobin A1C of greater than or equal to 6.5%, type 1 or type 2 diabetes, use of weight loss medication (within 90 days), hypertension, pregnancy or breastfeeding, history of cardiovascular disease, pancreatitis, major depressive disorder within two years, history of suicide attempt, or malignancy diagnosed within past five years. Once individuals were passed via the screening process, they were randomized centrally using a Web response system to either self- administer once daily, liraglutide 3.0 mg subcutaneous injections or placebo (1:1) as an adjunct to IBT which was provided for both the control and placebo group.

Over the course of the first four weeks post randomization, the liraglutide dose was increased in weekly increments of 0.6 mg until the desired dose of 3.0 mg was achieved. Throughout the 56-week study period, participants attended clinic visits to monitor their

response to treatment and received 23 brief (15 minute) IBT counseling sessions. The program included recommendations for diet, physical activity, and behavioral changes. Diet recommendations were based on guidance provided from the US Department of Agriculture. Regarding exercise recommendations, participants were all initially prescribed 100 min/week of moderate-intense physical activity. Physical activity was increased by 25 minutes every fourth week, with an end goal of 250 min/week. Coprimary endpoints noted were a change in body weight (percent) from baseline and proportion of participants who lost greater than or equal to 5% of baseline body weight. Secondary confirmatory end points included the proportion of participants who lost >10% or >15% of baseline body weight at week 56 and the proportion who lost greater than or equal to 4% of baseline body weight at week 16 (Wadden, et al. 2020). Further secondary confirmatory end points included were changes from baseline to week 56 in waist circumference (cm), self-reported quality of life in relation to physical function, and cardiometabolic parameters (HbA1C, fasting plasma glucose, systolic and diastolic blood pressure, and lipids). Safety was assessed by using two separate observation periods while assessing adverse events presented by the participants, physical examination, resting pulse, electrocardiogram, and laboratory measurements.

After the 56-week period, 80.3% (N=118) received liraglutide 3.0 mg and completed the trial. With respect to 73.6% (N=140) who received the placebo and completed the trial. The estimated mean weight change after the 56-week period was -7.5% for the treatment group receiving liraglutide and -4.0% for the placebo group in regard to both groups receiving intensive behavioral therapy (P=0.0003). The proportion of individuals who achieved greater than or equal to 5% weight loss at the end of trial was 61.5% with liraglutide and 38.8% with placebo (P=0.0003). The proportions with lost >10% were 30.5% (liraglutide) and 19.8% (placebo)

(P=0.0469), and >15% were 18.1% (liraglutide) and 8.9% (placebo) (P=0.0311), respectively (Wadden, et al. 2020). Considering cardiometabolic parameters and assessments of physical activity and function, significant changes were observed for both groups, however, was significantly improved with the treatment group. These parameters are noted above. Safety was measured as well and overall, liraglutide 3.0 mg combined with IBT was well tolerated and adverse events were consistent with the already established safety profile of liraglutide. No further safety measures were identified over the course of the study. The most frequent adverse effects included gastrointestinal events to include nausea, constipation, diarrhea, vomiting, and abdominal discomfort. Three acute gallstone disease events occurred; however, no events of pancreatitis were noted. Strengths of this study included a large sample of participants, use of a double-blind placebo-controlled design, and the addition of intensive behavioral therapy. Limitations of this study include a large majority of participants were white males, length of study was limited to just over one-year, and diabetic individuals were excluded from the study. A major limitation that was identified was the inability to determine the precise amount of IBT is needed to achieve clinically significant weight loss when combined with a pharmaceutical such as liraglutide (Wadden, et al. 2021). Another factor that may be considered as a limitation is this trial was the sponsorship by Novo Nordisk. Who developed the study protocol, supplied the trial drugs, planned, and performed statistical analyses, and provided writing assistance.

In further discussion, individuals with obesity and received liraglutide plus IBT was quite superior compared to the individuals who were apart of the placebo group in producing a clinically significant weight loss of greater than or equal to 5% from baseline weight. Those who were treated with liraglutide and IBT, compared to the placebo, achieved significantly greater

reduction in cardiometabolic risk factors to include waist circumference (cm), HbA1c, and fasting glucose.

In regard to the addition of IBT in both tested groups, the findings proved effectiveness in that half of the participants in both the treatment and placebo groups. Groups achieved the IBT weight loss criterion (greater than or equal to 3 kg) at 6 months with brief counseling. This was notably increased with the treatment group receiving liraglutide, 3.0 mg. Results from this study does show a concern with the extent in which high-intensity behavioral therapy (14-15 sessions within 6 months) contributes to additional weight loss when compared to the current study of monthly lifestyle counseling. As this was the second study performed at this time, additional trials are needed to be conducted and performed in order to yield further insight into these concerns. Overall, results of this study did produce a significant change in weight loss management for those receiving liraglutide 3.0 mg in addition to receiving intensive behavioral therapy when compared to the placebo group combined with intensive behavioral therapy. (Wadden, et al. 2021)

Lundgren, et al. (2021) conducted a randomized, head-to-head, placebo-controlled trial at Hvidovre Hospital and the University of Copenhagen, Denmark that enrolled non-diabetic obese adults (age 18-65) with a basal metabolic rate (BMI) of 32-43 kg/m2 who were randomly assigned for one year to one of four strategies: a moderate-to-vigorous-intensity exercise program plus placebo (exercise group); treatment with liraglutide (3.0 mg per day) plus usual leisure activity (liraglutide group); exercise program plus liraglutide therapy (combination group); or placebo plus usual leisure activity (placebo group) (Lundgren, et al. 2021). Individuals who were chosen to participate in the study were instructed to follow a low-calorie diet (800 kcal per day) for an initial 8 weeks. Those who had a weight loss of at least 5% from their baseline

body weight were then further randomly assigned in a 1:1:1:1 ratio to one of the following strategies as listed above for one year. In addition to participation of the strategies, all of the participants were instructed to attend 12 individual consultations that included measurement of body weight (kg) and dietetic support.

The primary endpoint of this study was a change in body weight from baseline measurements. The secondary endpoint of a change in body-fat percentage from baseline. The percentage of body fat was measured with the use of dual-energy x-ray absorptiometry in three separate phases; prior to initiating the low-calorie diet, at randomization, and at week 52. Prespecified metabolic health-related end points included changes from randomization to week 52 in fat mass, lean mass, cardiorespiratory fitness, glycated hemoglobin level, indexes of insulin resistance during fasting and meal intake, lipid levels, quality of life, waist and hip circumferences (cm), waist-to-hip ratio, blood pressure, and resting heart rate (Lundgren, et al. 2021). Those who participated in the exercise group was programed and designed to meet the World Health Organization (WHO) recommendations on physical activity. The participants were assigned to an instructor who planned and monitored each of the participants programs. In regard to medication of liraglutide administration, this was injected subcutaneously with a starting dose of 0.6 mg per day. Supervised weekly increments of 0.6 mg per day were initiated until the desired dose of 3.0 mg per day was obtained. Following the 8-week low-calorie diet, 195 participants underwent randomization. In the exercise group, 83% (N=48) were assigned, 84% (N=49) in the liraglutide group, 92% (N=49) in the combination group, and 82% (N=49) in the placebo group.

After the 52 weeks, all the active-treatment strategies led to a greater weight loss when compared to the placebo. The exercise group were down an average of -4.1 kg from baseline

body weight (P=0.03), liraglutide group was down -6.8 kg (P<0.001), combination group was down -9.5 kg (P<0.001), and the placebo group was down -2.7 kg (P=0.004) from baseline bodyweight. The mean total weight loss prior to the 8-week low-calorie diet to the end of the 52 weeks was approximately 15.7% of the baseline body weight in the combination group, 10.9% in the exercise group, 13.4% in the liraglutide group, and 6.7% in the placebo group. When reviewing changes in body-fat percentage, the combination strategy was superior compared to the three other strategies. The body fat percentage was greater in the exercise group compared to the placebo group with a treatment effect of -2.2% (P=0.004), was greater in the liraglutide group compared to the placebo group with a treatment effect of -2.0% and finally showed a greater effect from the combination group compared to the placebo group with a treatment effect of -3.9%. Body-fat percentage was further reduced in the combination group by -1.7% when compared to the exercise group (P=0.02) and by -1.9% when comparing the combination group to the liraglutide group (P=0.009) (Lundgren, et al. 2021).

All active treatment groups represented a decrease in fat mass and waist circumference (cm) in comparison to increases with the placebo group as well as reductions in the systolic and diastolic blood pressures. Exercise represented an increase in lean muscle mass. Exercise and the combination strategy were both associated with an increase in cardiorespiratory fitness which, however, was not observed with the placebo nor the liraglutide group. The liraglutide and the combination strategy both showed reductions in the glycated hemoglobin level when compared to an increase noted in the placebo group. A major strength of this trial was the flexibility and structure of the exercise program with monitoring of exercise adherence. Other strengths included the direct comparison of separate and combined effects of exercise and liraglutide as well as high quality assessments of body composition and cardiorespiratory fitness. Limitations

of this trial included that the results are not generalizable to those >65 years of age, individuals with a BMI >43, patients who are diabetics, and those who may have a low adherence or those who were limited to participate in the exercise program. A secondary limitation involves the sponsorship of the trial, Novo Nordisk. Who ultimately supplied the pharmaceutical, liraglutide, placebo injector pens, and the Cambridge Weight Plan supplied diet replacement products that were used over the course of the 8-week low calorie diet phase. Overall, the combination strategy of liraglutide and an exercise program was shown to be more effective in improving weight loss and decreasing the risk of cardiovascular disease and all-cause mortality when compared to either treatment alone. (Lundgren, et al. 2021)

Safety and Efficacy of Liraglutide with respect to long-term weight management

Two clinical trials, lasting 56 weeks, were conducted by le Roux, et al. (2017) that consisted of a randomized, double-blind, placebo-controlled, multicenter trials that sought out to investigate whether the efficacy and safety of liraglutide 3.0 mg injection differed between two subgroups of individuals with classified obesity or those who were classified as “overweight”, depending on body mass index (BMI). This post-hoc analysis was performed to establish whether the efficacy of liraglutide, from a weight management perspective, persists in higher BMI subgroups. During the initial screening process, the participants were randomized in a 2:1 fashion to either once daily liraglutide or placebo. Those receiving liraglutide started with an initial dose of 0.6 mg, and this dose was increased by 0.6 mg every week over the course of weeks 1-4 until the desired dose of 3.0 mg was achieved. Both groups involved adults (greater than or equal to 18 years of age), however one group consisted of those whose BMI ranged from 27 to <35 kg/m2, with the other group having a BMI of greater than or equal to 35 kg/m2. All

participants in both trials were advised by a dietician through individual or group counseling on diet and exercise. All were placed on a 500 kcal/day-deficit diet and instructed to perform greater than or equal to 150 minutes per week of exercise that was re-enforced with the use of pedometers. Participants body weight was recorded to the nearest 0.1 kg and was measured as well in an overnight fasting state. One trial, however included primarily individuals without type 2 diabetes and the other trial included primarily individuals with type 2 diabetes. Secondary endpoints were evaluated throughout both trials to include waist circumference (cm), hemoglobin A1C%, fasting plasma glucose, and blood pressure. Approximately 3,662 participants (n=1,279 overweight category, n=2,383 obese category) were associated with the trial of those with type 2 diabetes and 623 participants (n=273 overweight category, n= 350 obese category) were associated with the trial of those without type 2 diabetes.

In regard to efficacy, at the end of both 56-week trials, significantly greater weight loss was achieved from baseline on treatment with liraglutide 3.0 mg when compared to placebo in individuals with or without type 2 diabetes. Analysis of the interaction between treatment effect and baseline BMI subgroup (27 to <35 and greater than or equal to 35 kg/m2) revealed no evidence that the effect of liraglutide 3.0 mg on body weight differed between the two baseline BMI subgroups ($p>0.05$) (le Roux et al. 2017). There were significantly more individuals (without and with type 2 diabetes) who achieved greater than or equal to 5%, 10%, and 15% of categorical weight loss with liraglutide 3.0 mg compared to those with placebo. There was no evidence to suggest that the effect of liraglutide 3.0 mg on weight loss differed between the two baseline BMI subgroups ($p> 0.05$). Regarding the secondary endpoints, there were greater improvements seen with the liraglutide 3.0 mg group compared to the placebo from baseline in both trials. A majority of secondary endpoints revealed no evidence that the effects of liraglutide

3.0 mg differed between the BMI subgroups ($p>0.05$). However, individuals without type 2 diabetes did show greater improvement vs. placebo in the Impact of Weight on Quality of Life-Lite questionnaire related to physical function was noted in individuals who were associated with the obese group (greater than or equal to 35 kg/m2 BMI) ($p= 0.04$).

In regard to safety, adverse effects were fairly similar across all BMI subgroups. Rates of gallbladder disorders were low but did show a minor elevation with liraglutide 3.0 mg vs. placebo and the frequency of these outcomes were similar in comparison to all groups. Those who experienced acute pancreatitis were commonly seen with the liraglutide 3.0 mg group vs. placebo. The most frequently reported adverse effects were gastrointestinal in nature to include nausea and vomiting. Strengths that were associated with these two trials includes a large sample size, low exclusion criteria, and a direct comparison of two BMI subgroups and the effectiveness of liraglutide with associated lifestyle changes. Limitations of these analyses include the tests for interaction between the treatment group and baseline BMI were not adjusted for multiplicity and secondly, the SCALE program that was used was not designed to detect differences between subgroups and to test for interaction between treatment group and baseline BMI.

In conclusion of these two trials, there was no associated difference in the treatment efficacy or safety profile of liraglutide 3.0 mg for individuals with a BMI of 27 to <35 or greater than or equal to 35 kg/m2. However, given the treatment effects of liraglutide 3.0 mg are comparable in both BMI subgroups, liraglutide 3.0 mg can be a considered pharmaceutical agent for treatment across the higher and lower classes of obesity in association to lifestyle management. (le Roux, et al. 2017)

Ard, et al. (2016) conducted five double-blind randomized, placebo-controlled trials consisting of 5,325 adults (greater than or equal to 18 years of age) of racial subgroups with a

body mass index (BMI) of greater than or equal to 27 kg/m2 plus one or more comorbidity or individuals with a BMI of greater than or equal to 30 kg/m2 to determine the efficacy and safety of liraglutide 3.0 mg for chronic weight management vs. placebo in adjunction to diet and exercise modifications. Three trials were approximately 56 weeks in length, one trial 32 weeks, and the last being 52 weeks in length. Racial subgroups were broken down as white, black/African American, Asian, and other. The other subgroup includes American Indian or Alaska Native, Native Hawaiian people, or other Pacific Islanders. All of which were self-reported by the participants. Participants received either once-daily subcutaneous injections of liraglutide, starting at a dose of 0.6 mg with weekly increments of 0.6 mg until the final dose of 3.0 mg was achieved or placebo injections. Diet and exercise guidance was provided to participants in monthly intervals. Mean and categorical weight related end points were assessed to include greater than or equal to 5% weight loss from baseline, >10%, and >15%. Health related quality of life was assessed using the Impact of Weight on Quality of Life-Lite questionnaire. Safety variables such as pulse and overall adverse events were measured as well.

Primary endpoints that were assessed included body weight change from baseline (kg), BMI (kg/m2), and waist circumference (cm). Secondary endpoints included assessment of blood pressure, pulse, lipid panel, and glycemic variables to include hemoglobin A1C and fasting plasma glucose. At the end of all five trials, there were significant differences in the numbers of individuals apart of the separate racial subgroups with white participants outnumbering non-white participants, most of which were female. A mean BMI and change in body weight from baseline was shown the lowest in the Asian racial subgroup and the highest in the black/African American racial subgroup.

In regard to efficacy of liraglutide vs. placebo, this had shown a greater relative mean and weight loss from baseline when in comparison. Significantly more individuals from all racial subgroups lost greater than or equal to 5% (p=0.17), >10% (p =0.07), and >15% (p=0.23) of their baseline body weight who participated in the liraglutide group. Those who were apart of the treatment group receiving liraglutide 3.0 mg, the white racial group showed a -7.7% change of body weight from baseline, black/African American group showed a -6.3% from baseline, Asian group showed a -6.3% change, and the "other" group showed a -7.3% change from baseline body weight. Within the placebo groups there was a -2.3% change from baseline body weight seen in the white group, in the black/African American there was a -1.4% change, in the Asian group there was a -2.5% change, and lastly in there was a -0.49% change from baseline body weight seen with the "other" group. However, the mean and categorical weight loss effects did not show any dependence on racial subgroup as each race who received treatment of liraglutide resulted with an interaction p value of > 0.05.

Overall, the treatment differences were shown to be similar across all racial subgroups (Ard, et al. 2016). Greater mean reduction in the cardiovascular risk markers listed as secondary endpoints above were seen with the liraglutide 3.0 mg group vs. placebo in each racial subgroup. Health related quality of life did show improvement with the liraglutide treatment and the beneficial treatment effects of liraglutide 3.0 mg on quality of life was similar across all racial subgroups. The race-treatment interaction test was non-significant for total score (p=0.13), and physical function (p=0.56) of the quality-of-life questionnaire as well as for the physical component summary (p=0.36), mental component summary (p=0.98) and physical function (p=0.34) (Ard, et al. 2016).

With the safety portion that was assessed with these five trials, a portion of individuals who reported overall adverse events was quite similar across all groups. The most frequently reported event was gastrointestinal in nature with participants apart of the treatment group receiving liraglutide vs. placebo. The results of these five trials did in fact show the effects from liraglutide 3.0 mg on weight management, cardiovascular risk markers, and side effects were consistent across all racial subgroups that participated. Strengths of this study included large sample sizes across all racial subgroups, use of individual participant data from each trial as opposed to typical meta-analysis, and limited exclusion criteria. Limitations of these trials include the trials were unfortunately not designed or powered for comparisons across racial subgroups, and there was quite a disproportion of individuals within each group with white having the larger sample size. A secondary limitation is the trials were all funded by Novo Nordisk who also provided the pharmaceutical products used.

In conclusion to these trials, efficacy and safety was seen primarily with the use of liraglutide 3.0 mg for weight management with overall consistent positive effects on body weight, cardiometabolic factors, and health related quality of life across all racial subgroups which were assessed. (Ard, et al. 2016)

Pi-Sunyer, et al. (2015) conducted a 56-week trial that was aimed to evaluate the efficacy and safety of 3.0. mg of liraglutide injection in adjunction to reduced calorie diet and increased physical activity in regard to weigh management in overweight or obese adults who were non-diabetics. The study was analyzed above, however in the efficacy and safety profile will be discussed here. Post the 56-week period of the trial, random assignment in a 1:1 ratio was initiated for participants to either continue receiving liraglutide or switch to placebo for 12 weeks to assess whether efficacy was maintained after the discontinuation of the pharmaceutical and

safety issues related to discontinuation were addressed as well. Patients originally in the placebo group at the beginning of trial continued to receive placebo. The prespecified efficacy analysis used data from a full analysis set that did include all patients who underwent randomization and received at least one dose of the studied drug and had at least one assessment after baseline evaluated. The safety analysis set included all patients who received liraglutide. For weight management, only fasting measurements were obtained.

Regarding adverse events and the safety profile of this study, the most common side effects were noted in the liraglutide group and was primarily gastrointestinal in nature to include nausea, diarrhea, constipation, vomiting, dyspepsia, and abdominal pain. Gallbladder related events were common with the treatment group in comparison to placebo occurring in 61/2481 patients, including cases of cholelithiasis or cholecystitis. The weight loss that was noted among patients with gallbladder related adverse events was noted to be significantly greater compared to the mean weight loss in the entire population of participants. The rates of adverse events of pancreatitis and neoplasms were calculated from the period of treatment start until the final contact with the patient. Approximately 11 cases of pancreatitis were confirmed with 10/2481 patients in the liraglutide group and 1/1242 patients in the placebo group. There was a notable increase in mean lipase and amylase activity which was appreciated from baseline until week 56 of trial. Mean resting pulse was notably increased within the treatment group receiving liraglutide by the end of trial. The rates of cardiac arrythmia were similar across both studied groups, however tachycardia was higher in the treatment group vs. the controlled group. There were no clinically relevant differences seen between the two groups with respect to mental health assessments to include adverse events in relation to psychiatric disorders and questionnaire-

based depression or suicidal scores (Pi-Sunyer, et al. 2015). Spontaneous hypoglycemia was reported by 32/2481 patients within the treatment group receiving liraglutide and by 13/1242 patient within the controlled group receiving the placebo. No events of hypoglycemia were serious in nature.

Overall, the safety profile of liraglutide was consistent with findings from previous reports. The gastrointestinal disorders are common and were noted to be mostly transient side effects of the treatment. There were beneficial effects in relation to cardiometabolic variables and blood pressure seen within the treatment group. This data can be found above in a previous analysis of this study. In conclusion, the safety and efficacy of 3.0 mg injection the GLP-1 receptor agonist, liraglutide, in conjunction with diet and exercise was associated with a significant weight loss reduction in overweight or obese individuals. (Pi-Sunyer, et al. 2015)

Overview of Semaglutide in the use of weight management

Wilding, et al. (2021) conducted a randomized, double-blind, placebo-controlled trial at 129 sites in 16 countries to included Asia, Europe, North America, and South America to assess whether adults with a body mass index of 30 or greater can achieve weight loss with once-weekly injection of semaglutide at a dose of 2.4mg in adjunct to lifestyle intervention of diet and exercise. The study included 1,961 adults (>18 years of age) with a BMI of 30 or greater or those with a BMI of 27 or greater with underlying comorbidities (i.e., hypertension, dyslipidemia, obstructive sleep apnea, chronic obstructive pulmonary disease, nonalcoholic fatty liver disease, polycystic ovarian syndrome, or coronary artery disease) were placed at random (2:1 ratio) to complete 68 weeks of treatment or a matching placebo. After the 68-week period, this was then

followed by a 7-week period without the receipt of semaglutide, placebo, or lifestyle intervention.

The primary endpoint of the study was the percentage change in body weight from baseline to week 68. Analysis from the dual energy x-ray absorptiometry (DXA) substudy measured the body composition of each individual to include total fat, total lean body mass, and regional visceral fat mass. As a result, 94.3% completed the trial (treatment N=1306, placebo N=655). In the semaglutide group, the estimated mean weight change at week 68 was-14.9% (average 15.3kg) compared to -2.4% (average 2.6kg) with placebo. Participants who received semaglutide are more likely to lose 5% or more of their baseline body weight than those who received the placebo ($P<0.001$). Supportive secondary end points show semaglutide was associated with greater reductions in waist circumference, BMI, and systolic and diastolic blood pressure. Benefits favoring semaglutide were noted to show changes in glycated hemoglobin, fasting plasma glucose, C-reactive protein, and fasting lipid levels. Strengths of this trial include a large sample size and high rate of adherence to the treatment as well as completion of the trial. Limitations include the sample size was predominantly women and White participants, a relatively short duration of trial, exclusion of individuals with type 2 diabetes, and the potential the participants enrolled may show a greater commitment to weight loss efforts than the general population. Furthermore, this study did not specify or disclose into what lifestyle intervention/modifications were adjusted and how compliance was monitored resulting as a limitation. This trial is supported for Novo Nordisk which portrays as a limitation to this study overall as well as a potential bias.

Currently, approved anti-obesity drugs that are on the pharmaceutical market require multiple administrations throughout the week compared to semaglutide once-weekly regimen which may improve adherence. (Wilding, et al. 2021).

Blundell, et al. (2017) conducted a randomized, double-blind, placebo-controlled study that investigated the effects in regard to appetite, energy intake, and weight loss with the use of once-weekly semaglutide, 1.0 mg, in adults with obesity. Inclusion criteria included adults who were greater than or equal to 18 years of age, body mass index (BMI) of 30-45 kg/m2, hemoglobin A1C <6.5%, and a stable body weight. Exclusion criteria included diagnosis of type 1 or type 2 diabetes mellitus, history of chronic or acute pancreatitis, history of medullary thyroid carcinoma, previous bariatric surgery, tobacco or nicotine use, and anticipated change in lifestyle during the trial. The trial itself consisted of two 12-week crossover treatment periods. Randomization of participants were performed in a 1:1 ratio to either receive treatment or placebo. Those receiving semaglutide, the starting dose was 0.25 mg which was given for 4 weeks, then escalated to 0.5 mg for another 4 weeks, and the final 4 weeks of trial, the dose increased to the desired dose of 1.0 mg.

The primary endpoint to this study consisted of ad libitum energy intake, meaning the participants were allowed to eat without restriction, during their lunch meal after 12 weeks of treatment. Secondary endpoints included ad libitum energy intake during participants evening meal, energy intake, and ratings of appetite parameters such as hunger, fullness, satiety, thirst, nausea, and well-being before and after a breakfast meal. Food preferences, body weight, and body composition was measured and assessed as well. At the end of the 12-week period, participants were standardized with regard to meals, physical activity, and sleep. Body

composition was measured in a fasted state using air displacement plethysmography. Approximately 30 participants were screened, and 28 adults completed the trial. Within regard to energy intake and macronutrient composition, ad libitum energy intake was approximately 35% lower with the treatment group of semaglutide vs. placebo ($p<0.0001$). Total energy intake across all ad libitum meals was 24% lower with semaglutide ($p<0.0001$). Overall appetite suppression was scored higher with semaglutide vs. placebo, indicating less appetite is seen with the treatment group ($p=0.0023$). Ratings for thirst, nausea, and well-being was similar between all groups. There was a notable difference with control of satiety, portion size, and food cravings seen with the treatment group vs. placebo with the aid of the Control of Eating Questionnaire (COEQ).

In reference to body weight and body composition, a change from baseline means body weight of -5.0 kg with treatment vs. +1.0 kg with placebo. Noting a three-fold greater weight loss of mean body fat over lean body mass was observed with semaglutide. Strengths of this trial included the ability of participants to act as their own control, crossover design, and wide variability in observations with the use of this pharmaceutical agent. Limitations of this trial include a small and limited sample size, participants were primarily male, and this trial could also be limited using a crossover design. Overall, in conclusion of this trial, the data did indicate that semaglutide induced weight loss with the aid of reduced energy intake associated with reductions of appetite. Other mechanisms include improvements with control of eating and increase in satiety (Blundell, et al. 2017).

Rubino, et al. (2021) completed a randomized, double-blind, placebo-controlled withdrawal study lasting 68 weeks spanning across 73 separate sites in 10 countries in order to

compare the once-weekly use of semaglutide, 2.4 mg subcutaneous injection, to placebo for weight loss maintenance in conjunction to lifestyle intervention. This study consisted of 1,051 adults (greater than or equal to 18 years of age) with at least one unsuccessful dietary effort to lose weight. Participants are either in overweight with a body mass index (BMI) >27 kg/m2 with at least one treater or untreated weight-related comorbidity or obese with a BMI greater than 30 kg/m2. All participants initially received treatment of semaglutide 0.25 mg which increased every 4 weeks to the maintenance dose of 2.4 mg by week 16 and continued through week 20. At week 20, participants underwent randomization in a 2:1 ratio in a double-blind manner to either continue treatment or switch to placebo for 48 weeks. All participants received lifestyle intervention from week 0 to 68. This included monthly counseling by qualified health professionals, advised to a reduced calorie diet (500 kcal deficit), and increased physical activity to 150 minutes/week. All of which was self-recorded daily and reviewed during their monthly counseling visits.

The primary endpoint was a percent change in body weight from the week of randomization (week 20) to week 68. Secondary endpoints were change from week 20 to 68 in waist circumference, systolic blood pressure, diastolic blood pressure, absolute body weight (kg), hemoglobin A1C, fasting plasma glucose, fasting serum insulin, lipid levels, and physical functioning score on the Short Form 36 Version 2 Health Survey (Rubine, et al. 2021). During week 0-20, mean body weight declined by 10.6% and was accompanied by reductions in waist circumference, BMI, blood pressure, hemoglobin A1C, fasting plasma glucose, and improvements in lipid panels. At week 20, 803 participants were randomized (treatment n=535, controlled n=268). From week 20-68, the estimated mean weight change from baseline was -7.9% with the continued semaglutide treatment vs. +6.9% weight change from baseline with the

placebo group ($p<0.001$). Waist circumference (-9.7 cm) and BMI (-4.7) decreased from week 20 to 68 with continued semaglutide and increased with placebo ($p<0.001$). Blood pressure remained relatively stable with continued treatment and increased with placebo ($p<0.001$). Hemoglobin A1C, fasting plasma glucose, and lipid panel noted to show improvements with continued treatment group vs. placebo.

Regarding changes noted over the entire trial period (week 0-68), an estimated mean body weight change was approximately -17.4% with continued semaglutide vs. -5.0% with placebo. Common adverse events were associated with the treatment group and commonly gastrointestinal disorders (71.4%), most of which were mild in nature to include nausea, diarrhea, and vomiting. Strengths of this study include the withdrawal design, large sample size, blinded design, and high rates of treatment regimen and trial completion. Limitations of this study include inflexibility with the run-in period, no assessment of adherence to lifestyle interventions, and adverse events were counted only during the randomization period due to lessoning the potential effect of the long half-life of semaglutide.

In conclusion, the once-weekly treatment of semaglutide, 2.4 mg, had persistent weight loss vs. the placebo group who persisted to then gain weight. Results of this study emphasize the chronicity of obesity and that treatments such as these can maintain and amplify weight loss.

A trial performed by Davies, et al. (2021) analyzed weight management and loss with the use of GLP-1 analogue, semaglutide compared to placebo, in adults who are overweight or obese and have type 2 diabetes mellitus. Inclusion criteria included a body mass index (BMI) of at least 27 kg/m2 and glycated hemoglobin of 7-10% and individuals who had a prior diagnosis of type 2 diabetes mellitus. Exclusion criteria included self-reported changes in bodyweight of >5 kg within 90 days of screening, previous or planned bariatric surgery, or a weight loss device.

Coprimary endpoints included percentage change in bodyweight and achievement of weight reduction of at least 5% for a 68-week duration period. Secondary outcome consisted of patients achieving bodyweight reductions of at least 10% or 15% at week 68. Approximately 1,210 participants were randomly assigned in a 1:1:1 fashion, who either received semaglutide 2.4 mg (n=404), semaglutide 1.0 mg (n=403), or placebo (n=403). Treatment was administered once weekly for 68 weeks in conjunction to lifestyle intervention and then followed by a 7-week period without treatment. Lifestyle intervention consisted of dietary counseling (500 kcal reduction) and physical activity of a minimum of 150 minutes per week, all of which was self-reported. Height, bodyweight, waist circumference, blood pressure, and pulse rate were measured at baseline and were repeated every 4 weeks. Hemoglobin A1C, fasting plasma glucose, and fasting serum insulin was measured as well. At the end of trial, 391 participants receiving 2.4 mg semaglutide completed the trial, 390 particpants receiving 1.0 mg semaglutide completed trial, and 383 participants who received placebo completed the trial.

Mean bodyweight percentage change from baseline was found to be higher with the semaglutide 2.4 mg group with an average of -9.6% vs. -3.4% with placebo ($p<0.0001$). Patients were more likely to achieve at least 5% reduction in baseline bodyweight at week 68 with semaglutide 2.4 mg compared to placebo or semaglutide 1.0 mg ($p<0.0001$) (Davies, et al. 2021). Comparably, more participants achieved increased reductions of at least 10%, 15%, or 20% at the end of trial with semaglutide 2.4 mg when compared to either semaglutide 1.0 mg or placebo ($p<0.0001$). Significant benefits were seen with those receiving semaglutide 2.4 mg in regard to changes in waist circumference, systolic blood pressure, lipid profile, and inflammatory markers. Hemoglobin A1C was noted to improve across all groups. Improvement of fasting plasma glucose was noted throughout both treatment groups in compared to placebo.

Common adverse effects were similar to other known studies of GLP-1 analogues, primarily gastrointestinal disorders to include nausea, vomiting, diarrhea, and constipation. Most episodes were transient and mild to moderate in severity without significant relation to dosage or increase of dosage. Majority of patients were just able to continue the trial product and recovered appropriately. At the end of trial, more than two-thirds patients who were treated with semaglutide 2.4 mg achieved their targeted hemoglobin A1C% of 6.5% or less (Davies, et al. 2021). At least 5% of participants baseline body weight was lost by 69% of patients who were receiving semaglutide 2.4 mg dose in compared to 57% semaglutide 1.0 mg and 28% placebo. It was shown that semaglutide 2.4 mg was also effective in improving cardiometabolic risk factors as well as glycemic control in individuals with type 2 diabetes mellitus. Strengths of this study include a large sample size, double-blind design, lifestyle counseling, high rate of trial completion, and dose adjustment options. Limitations of this study include exclusion of patients who were utilizing insulin prior to trial, this trial was funded and sponsored by Novo Nordisk, and participants were predominantly white.

Overall, this study revealed that in adults who are either overweight or obese and have type 2 diabetes mellitus and receive once-weekly subcutaneous semaglutide 2.4 mg in conjunction to lifestyle intervention was more effective in reducing bodyweight in comparison to either group observed.

Safety and Efficacy of Semaglutide with respect to long-term weight management

An observational, retrospective study was performed by Pérez-Belmonte, et al. (2022), on obese patients (body mass index greater than 30 kg/m2) who had underlying type 2 diabetes mellitus and chronic heart failure to observe the use of subcutaneous semaglutide injections in adjunction to lifestyle modifications and weight loss management. Approximately 136 patients

were included in the study from baseline to 12 months in duration. Participants were started with a once-weekly dose of 0.25 mg semaglutide for an initial 4 weeks and was increased to 0.5 mg in 4 week increments until a maintenance dose of either 0.5 mg or 1.0 mg was achieved per healthcare professional recommendations. All patients were provided with diet and physical activity recommendations according to their functional class. Follow-up appointments were conducted at 3, 6, and 12 months after initiating the pharmaceutical.

A multitude of endpoints were measured at each follow up to include body weight (kg), BMI (body mass index), waist circumference, type 2 diabetic duration and treatment, heart failure duration and cause, ejection fractions, therapeutic and laboratory variables (serum creatinine, estimated glomerular filtration rate, basal fasting glucose, glycated hemoglobin, LDL, HDL, total cholesterol, triglycerides, uric acid, hematocrit, and brain natriuretic peptide. A primary endpoint which was evaluated the clinical efficacy of the patient's heart failure status in association to weight management with the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ) as the New York Heart Association (NYHA) classification. Secondary endpoints included the glycemic efficacy. From the initial baseline to the end of trial of 12 months, there was quite a significant improvement in the KCCQ score which increased from 59.0 points to 79.9 points ($p<0.01$) as well as a reduction of patients NYHA functional class from 40.4% to 16.2% ($p<0.01$). Regarding glycemic control, there was a significant reduction in fasting blood glucose and glycated hemoglobin (HbA1c%). Patients with a <7% HbA1c increased from 16.2% at baseline to 64.5% at 12 months ($p<0.001$). The evaluation of weight loss noted a significant reduction of body weight (12.7 kg) and BMI (7.1 kg/m2) with a decline in the proportion of patients with obesity to 50.8% (Pérez-Belmonte, et al. 2022). No changes

were observed with other laboratory evaluations. Minor adverse reactions were noted primarily to include gastrointestinal disorders.

Overall, this study found that in patients with obesity and type 2 diabetes and heart failure, semaglutide significantly improved their heart failure status and increased quality of life. Semaglutide was also found to be quite effective regarding glycemic control noting reductions in fasting blood glucose, HbA1c levels, and body weight. Patients were also found to experience a significant de-intensification of their type 2 diabetes treatment with reductions in the number of daily glucose-lowering drugs with good tolerability. A strength of this study includes many variables that were assessed throughout this study such as multiple anthropometric characteristics, glycemic control, heart failure status, treatment de-intensification, laboratory variables, and safety variables. Limitations of this study include a limited sample size, lack of a controlled group, and observational nature of the data.

The use of once weekly semaglutide significantly improved variables that were assessed throughout the study as well as the management of weight in obese patients with type 2 diabetes and heart failure. (Pérez-Belmonte, et al. 2022)

Direct comparison of Liraglutide vs. Semaglutide regarding efficacy and safety for weight management

Rubino, et al. (2022) conducted a 68-week long randomized trial across 19 United States sites that evaluated a comparison of liraglutide vs. semaglutide with respect to weight loss in overweight or obese adults. Adults (greater than or equal to 18 years old) with one or more self-reported unsuccessful dietary weight loss effort and a body mass index (BMI) of 30 kg/m2 or

greater or >27 kg/m2 with one or more weight related comorbidity such as hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease were eligible participants. Key exclusion criteria included participants with diabetes mellitus, hemoglobin A1C of 6.5% or greater, and self-reported body weight changes of greater than 5 kg approximately 90 days or less prior to screening. After the initial screening process participants were randomized in a 3:1:3:1 fashion to either receive once weekly semaglutide 2.4 mg, or matching placebo, or once daily liraglutide 3.0 mg, or matching placebo. Semaglutide was initiated at 0.25 mg and was increased to 2.4 mg over 16 weeks as the desired dosage. Liraglutide was initiated at 0.6 mg and was increased to 3.0 mg over 4 weeks as the desired dosage. All participants throughout each group received counseling from qualified healthcare professionals approximately every 4 to 6 weeks and were instructed to initiate a 500-kcal deficit diet as well as advised to increase physical activity to greater than or equal to 150 minutes per week.

The primary endpoint of this study was percentage change from baseline and body weight at week 68. Secondary end points were achievement of weight loss of 10% or more, 15% or more, and 20% or more by the end of trial from baseline body weight. Further supportive end points that were addressed throughout this trial were changes from baseline and absolute body weight, waist circumference, blood pressure, fasting lipid concentration, C-reactive protein, hemoglobin A1c, fasting plasma glucose, and glycemic status. At the end of trial, 94.4% (n=319) participants completed the trial from the 338 participants that were enrolled and randomized. Approximately 86.2% received the 2.4 mg dose of semaglutide (n= 126) and 95.7% received the 3.0 mg dose of liraglutide (n=127). At week 68, the estimated mean change in body weight was -15.8% with semaglutide and -6.4% with liraglutide ($p<0.001$). The proportions of participants

achieving 10% or more, 15% or more and 20% or more weight loss were 70.9%, 55.6% and 38.5% with semaglutide, and 25.6%, 12% and 6% with liraglutide, respectively (Rubino, et al. 2022). There was a significantly greater achievement of weight loss noted with the semaglutide group ($p<0.001$) from this perspective. The supportive end points that are noted above all favored the semaglutide group in respect to favorable reduction of numbers.

Adverse events that were reported throughout all groups were primarily noted to be gastrointestinal in nature that is consistent with other studies associated with these pharmaceutical agents. Most of these events were mild to moderate in severity. Gallbladder related disorders, mostly cholelithiasis, reported by 0.8% with semaglutide, and 3.1% with liraglutide, and 1.2% with placebo. More insomnia events occurred with liraglutide vs. semaglutide. There were also more discontinuations of the pharmaceutical that were adverse event related with the liraglutide group in comparison to the semaglutide group. Strengths of this trial include a large sample size, length of trial, and minimal exclusion criteria. Limitations of this trial include the response to poor tolerance of the maintenance dose differed, dosing differences, and lastly the study was primarily white and female participants. It was not only shown how effective one pharmaceutical agent is compared to another, but the safety profile of semaglutide was found to be more tolerable as well in comparison.

Among adults who are overweight or obese it was found that once weekly semaglutide compared to once daily liraglutide in conjunction to counseling for diet and physical activity, resulted in significantly greater weight loss, and accompanied by improvement in several cardiometabolic risk factors.

A study conducted by O'Neil, et al. (2018) compared the efficacy and safety profile of semaglutide vs. liraglutide in regard to weight loss in obese patients in conjunction to nutrition adjustments and physical activity. It was a randomized, double-blind, placebo and active controlled study performed at 71 clinical sites across 8 countries. Inclusion criteria included adults (18 years or older) without diabetes and with a body mass index (BMI) of greater than or equal to 30 kg/m2. Eligible individuals must have undergone at least one unsuccessful weight loss attempt. The participants were randomly assigned in a 6:1 ratio to each active treatment group or matching placebo. The study consisted of a 1-week screening period, 52 weeks of treatment, and 7 weeks of a post treatment follow up. Visits occurred every 2 weeks throughout the trial to assess body weight, vital signs, and adverse events. Participants were required to meet with a counselor to assess nutrition and physical activity. Eligible individuals were advised to follow a daily energy intake of a 500-kcal deficit. Participants were advised to perform physical activity at minimum 150 minutes per week.

The primary endpoint of this study was percentage change in body weight from baseline to week 52. Secondary endpoints consisted of weight loss of 5% or more or 10% or more of baseline, absolute change in weight, waist circumference, waist-to-hip ratio, BMI, change in glucose metabolism, and change in cardiovascular risk factors. Approximately 957 participants were randomly assigned with 102 participants per active treatment group and 136 per each placebo group. At the end of trial, 93% (n=891) of the patients completed the study. The estimated mean weight reduction from baseline two week 52 for participants receiving semaglutide ranged from 11.4% to 16.3%. The estimated weight reduction for the liraglutide group was 7.8% and 2.3% for the placebo group. Estimated weight loss of at least 5%, 10%, 15%, or 20% from baseline were dose dependent within the semaglutide group. Approximately

54 to 83% of participants receiving semaglutide 0.05mg – 0.4 mg in 4-weekly escalation groups had an estimated weight loss of 5% or more compared to 23% receiving placebo and 66% receiving liraglutide ($p<0.0001$). Approximately 19-65% of participants receiving semaglutide (0.05mg – 0.4mg) lost 10% or more bodyweight compared to 10% with placebo and 34% receiving liraglutide ($p<0.0001$).

In regard to the safety profile of these pharmaceuticals, the most common adverse events were gastrointestinal events seen with the treatment groups. Most of the reported events were mild or moderate in intensity. The most common seen events were nausea, diarrhea, constipation, and vomiting. As with the efficacy, the effect of semaglutide and the dose-escalation speed on safety outcomes was inconsistent (O'Neil, et al. 2018). Strengths of this study include a large sample size, few exclusion criteria, and this was also the first study to assess semaglutide for weight management as opposed to focusing on glycemic control in type 2 diabetics. Limitations of this study include assessing adherence to diet recommendations, body composition was not performed, and the difficulty of masking participants and staff to the assigned dose due to the dose-escalation periods. It was noted throughout the study that weight reductions were seen at higher doses of semaglutide and this persisted over the course of the 52 weeks. As compared to the findings of liraglutide which weight loss was noted to plateau at an earlier timepoint. Most of the secondary outcomes that are noted above were shown to improve with the semaglutide group, showing the effectiveness of this drug.

In regard to safety, the findings showed no dose dependency and were consistent with the data for other GLP-1 receptor agonists even with dose-escalations with the semaglutide group. Overall, semaglutide was well tolerated from an effective and safety profile by the

participants and therefore showed an appealing benefit to risk profile particular at the higher doses associate with greater weight loss.

Discussion

Obesity is an evident global health issue and a rising epidemic. In the US alone, the prevalence of higher obesity classes has increased by 70% over the past 10 years (le Roux, et al. 2021). With the aid of many pharmaceuticals such as liraglutide and semaglutide, we have seen improvement with these numbers. The end goal and solution to this ongoing issue in which healthcare professionals should strive for is long term weight loss management and sustainability in obese individuals. All studies reviewed above had an average trial duration of a year, so long term use of these pharmaceuticals is still in question. However, applicable insight was gathered based on the safety and efficacy of these medications as well as a thorough comparison to recognize which is superior in regard to weight loss management for adults with obesity.

The first question to assess is the safety of these medications regarding persistent weight loss. As both medications are glucagon-like peptide (GLP) 1 receptor agonists, the safety and adverse events were very similar in comparison. As they inhibit the glucagon secretions from pancreatic islets in a glucose dependent fashion, adverse events were primarily localized to the gastrointestinal system (O'Neil et al. 2018). Adverse events included nausea, vomiting, diarrhea, constipation, and abdominal pain were the most common symptoms verbalized from participants. Gallbladder events such as cholelithiasis or cholecystitis as well as pancreatic enzymes were noted to show minor elevations with an increase in dosage between the medications. Most episodes were transient and mild to moderate in severity (Pérez-Belmonte, et al. 2022). However, more commonly those who experienced such events were predisposed

depending on their current health status prior to treatment. Participants who did experience such adverse events were either able to continue the trial product and recovered well, or ultimately stopped the product all together to prevent further complications. Predominantly with semaglutide, the effectiveness and safety of the medication with dosage escalation was inconsistent across all trials. There was no dose dependency regardless of dose-escalations and the effect on the safety profile throughout the weeks of trial (O'Neil, et al. 2018). In a direct comparison via a study performed by Rubino, et al. (2022), events of cholelithiasis were reported by 0.8% who were apart of the semaglutide group and a 3.1% apart of the liraglutide group. Insomnia commonly occurred within the liraglutide group and participants who experienced adverse related events within this group were noted to discontinue the drug in comparison to semaglutide. Ultimately, electing semaglutide as the more tolerable medication for most of the participants in a direct comparison. Specific contraindications that have been distinguished against use of these medications are individuals with a prior history of pancreatitis as post marketing reports from the studies analyzed have shown cases of reoccurrence of hemorrhagic and non-hemorrhagic pancreatitis. If the patient does not have a past medical history of pancreatitis and has an acute onset while on the medication, it should be stopped immediately and not readministered. The use of liraglutide, semaglutide, or other GLP-1 receptor agonists should not be used with patients who have a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia (Blundell, et al. 2017). All in all, it must be determined the safety with long term use of these pharmaceuticals, especially if it has been elected by the provider to keep individuals on these medications long term for weight loss management or other

comorbid reasons. Further trials and evaluation are needed to be performed and assessed in the future (Pi-Sunyer, et al. 2015).

The second question to further evaluate, is the inquiry of efficacy between the two medications and weight loss management in the obese population. Specifically analyzing the efficacy of liraglutide first, it was shown to be superior when compared to placebo with an average mean weight loss of 6.3-8.0% from baseline body weight across all trials. A dosage of 3.0 mg was the average dose utilized throughout most of the trials that were analyzed. This dose specifically, represented the highest total of weight lost across the participants regardless of baseline body mass index. In a study performed by Pi-Sunyer, et al. (2015), a total of 63.2% of patients in the liraglutide, 1 mg dosage, group compared to 27.1% in the placebo group lost at least 5% of their body weight from baseline ($p<0.001$), and 33.1% lost more than 10% of their body weight from baseline ($p<0.001$) (Pi-Sunyer, et al. 2015). It was found though with the use of liraglutide in conjunction with lifestyle modifications as well as intensive behavioral therapy, there was an even greater loss of mean body weight regardless of if participants were a part of the treatment or control group. In this specific study, the proportion of individuals who achieved greater than or equal to 5% weight loss at the end of trial was 61.5% with liraglutide and 38.8% with placebo ($p=0.0003$), those who lost >10% were 30.5% (liraglutide) and 19.8% (placebo) ($p=0.0469$), and those who lost >15% were 18.1% (liraglutide) and 8.9% (placebo) ($p=0.0311$), respectively (Wadden, et al. 2020). Along with a percentage of weight loss seen with the use of liraglutide, secondary endpoints to include decrease in waist circumference, glycemic control, and cardiometabolic markers were found to be superior when compared to placebo.

In considering semaglutide and its efficacy with weight loss management, it was found to be significantly superior compared to placebo throughout all trials within this project. A mean weight change across all literature analyzed was noted to be between 7.9-17.4% weight loss from baseline body weight. Studying semaglutide specifically and the dosage of the medication vs. weight loss, it was found that participants lost more weight at a consistent dose of 2.4 mg versus 1.0 mg. At least 5% of participants baseline body weight was lost by 69% of those receiving the 2.4 mg dose vs. 57% of those receiving the 1.0 mg dose (Davies, et al. 2021). With continued use of semaglutide, primarily seen at the 2.4 mg dose, a significant change in body weight was noted within the first couple months of use. However, on average by month four, it was commonly seen to show a plateau in persistent weight loss across most participants. On average, a loss of 10.6% was seen from 0-20 weeks. Through weeks 20-68, an average loss of 7.9% was seen with those who were consistent with medication use and made the required adjustments of lifestyle measures (Rubine, et al. 2021).

Furthermore, after analyzing the two pharmaceuticals throughout all studies that were executed, they both were shown to be superior when compared to the control groups with respect to weight loss. They both had shown reductions in cardiometabolic risk factors to include waist circumference, blood pressure, fasting lipids, improved glycemic control, and inflammatory markers regardless of diabetic status. In a study performed by Rubino, et al. (2021), an average of 9.7 cm decrease in waist circumference was seen predominantly with patients apart of the semaglutide group ($p<0.001$). While both medications did show reductions in the above secondary endpoints, semaglutide was the favored group due to satisfactory outcomes and better tolerability and compliance with medication usage.

Lastly, a direct comparison between liraglutide and semaglutide had shown favor towards semaglutide particularly for its effectiveness with weight management, but also for its favorable decrease in further cardiometabolic factors. In a comparison study performed by Rubino, et al. (2022), at the end of a 68-week period those receiving 2.4 mg of semaglutide lost an average of 15.8% from their baseline body weight compared to 6.4% loss with liraglutide ($p<0.001$). Within this study, those who lost >10% of their bodyweight was demonstrated within the semaglutide group of 70.9% of participants compared to 25.6% within the liraglutide group ($p<0.001$). In a separate study conducted by O'Neil, et al. (2018), the estimated weight reduction from the patient's baseline weight was 11.4% with semaglutide and 7.8% with liraglutide. Both pharmaceuticals were shown to be more effective with weight loss at higher dosages in conjunction to lifestyle modifications, however significant findings of dosing patterns were found with the semaglutide group specifically. In combination to lifestyle modifications of diet and physical activity, semaglutide was found to not only be more tolerable, but also revealed clinically relevant weight loss when compared to liraglutide. Participants who were apart of the semaglutide group had preferred this medication in regard to administration of the medication in comparison to liraglutide. As semaglutide is a once-weekly subcutaneous injection versus liraglutide is a once-daily subcutaneous injection. This represented an increase in adherence from patients which ultimately provided better data when investigating the efficacy and safety of use.

Overall, the literature reveals the use of semaglutide has been found to be the preferred pharmaceutical over liraglutide in regard to weight loss management in obese individuals. Both pharmaceuticals have shown to represent reductions in body mass index, cardiometabolic risk factors, and over well-being. Furthermore, both were found to be more effective in adjunction to

an increase in physical activity and dietary changes throughout all groups of individuals. However, as noted before the average length of trials that were studied ranged from 52-68 weeks. To ensure these medications may be used for an extended period as well as are safe and effective, it was determined through a majority of trials that long-term studies and clinical trials are needed to be implemented to further answer this question.

Conclusion

Obesity is a complex condition affecting a multitude of systems with serious social and psychological dimensions. Lifestyle modifications of dietary adjustments and exercise have been deemed to be the most attainable and healthy form of weight loss, however within the obese population, there has been a significant struggle to initiating weight loss. Both GLP-1 receptor agonists studied here, liraglutide and semaglutide, have been deemed to be effective and safe agents in regard to weight loss management. Further benefits have been recognized with the use of pharmacotherapy to include cardiometabolic biomarkers, glycemic control for both diabetic and non-diabetic individuals, and significant improvements with patient's overall mental health. As noted from the literature reviewed, semaglutide was discovered to be the preferred agent from a persistent weight loss perspective and this agent was the most tolerable medication noted from the participants. Furthermore, the question of long-term use is still in consideration. Additional future research focusing on long-term use of these medications is needed to be pursued to ensure the medications are safe and effective long term.

Application to Clinical Practice

Obesity is known to be a major contributor to some of the leading causes of death in the United States including diabetes, heart disease, and various categories of cancer. In applying this

knowledge to practice, it must be considered that initiating these pharmaceuticals to an obese individual may be aiding in the sole aspect of weight loss, however this may also lead into further underlying comorbid conditions such as hypertension, type 2 diabetes, and other various metabolic syndromes. Ultimately it has been determined via literature analyzed for this comprehensive review, as well as first-hand accounts with professionals within this field that long term data is still needed. A secondary confrontation that has been addressed is patient coverage of these pharmaceuticals, particularly for weight loss purposes. Physicians associates and other related medical practitioners know of certain pharmaceuticals that have been approved for such applications. However, with up-and-coming medications that have been found to be superior in the sole aspect of weight loss such as semaglutide injectables, it has been difficult to have these medications approved for their own indications, let alone for the linear purpose of weight loss. In the meantime, how physician associates can apply what is known currently to out practices as providers is to ultimately to do what is right for our patients. This is highlighted by finding what may work best individually per patient through a consistent and measured approach and further resources they can utilize to ultimately achieve their goals for their health and overall well-being, whether that be with or without the use of pharmaceuticals. With the aid of further research into long term management with the use of pharmaceutical agents in conjunction to lifestyle modifications as well as possibly initiating behavioral therapy, we will be on the right path to making a healthy change and lowering the progression to this rising epidemic.

References

Aaseth, J., Ellefsen, S., Alehagen, U., Sundfør, T., & Alexander, J. (2021). Diets and drugs for weight loss and health in obesity – An update. *Biomedicine & Pharmacotherapy*, *140*, 111789. https://doi.org/10.1016/j.biopha.2021.111789

Ard, J., Cannon, A., Lewis, C., Lofton, H., Vang Skjøth, T., Stevenin, B., & Pi-Sunyer, X. (2016). Efficacy and safety of liraglutide 3.0 mg for weight management are similar across races: subgroup analysis across the SCALE and phase II randomized trials. *Diabetes, Obesity and Metabolism*, *18*(4), 430–435. https://doi.org/10.1111/dom.12632

Ard, J., Fitch, A., Fruh, S., & Herman, L. (2021). Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. *Advances in Therapy*, *38*(6), 2821–2839. https://doi.org/10.1007/s12325-021-01710-0

Blundell, J., Finlayson, G., Axelsen, M., Flint, A., Gibbons, C., Kvist, T., & Hjerpsted, J. B. (2017). Effects of once weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes, Obesity and Metabolism*, *19*(9), 1242–1251. https://doi.org/10.1111/dom.12932

Davies, M., Færch, L., Jeppesen, O. K., Pakseresht, A., Pedersen, S. D., Perreault, L., Rosenstock, J., Shimomura, I., Viljoen, A., Wadden, T. A., & Lingvay, I. (2021). Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2

diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *The Lancet*, *397*(10278), 971–984. https://doi.org/10.1016/s0140-6736(21)00213-0

le Roux, C., Aroda, V., Hemmingsson, J., Cancino, A. P., Christensen, R., & Pi-Sunyer, X. (2017). Comparison of Efficacy and Safety of Liraglutide 3.0 mg in Individuals with BMI above and below 35 kg/m^2: A Post-hoc Analysis. *Obesity Facts*, *10*(6), 531–544. https://doi.org/10.1159/000478099

Lundgren, J. R., Janus, C., Jensen, S. B., Juhl, C. R., Olsen, L. M., Christensen, R. M., Svane, M. S., Bandholm, T., Bojsen-Møller, K. N., Blond, M. B., Jensen, J. E. B., Stallknecht, B. M., Holst, J. J., Madsbad, S., & Torekov, S. S. (2021). Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. *New England Journal of Medicine*, *384*(18), 1719–1730. https://doi.org/10.1056/nejmoa2028198

O'Neil, P. M., Birkenfeld, A. L., McGowan, B., Mosenzon, O., Pedersen, S. D., Wharton, S., Carson, C. G., Jepsen, C. H., Kabisch, M., & Wilding, J. P. H. (2018). Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomized, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *The Lancet*, *392*(10148), 637–649. https://doi.org/10.1016/s0140-6736(18)31773-2

Pérez-Belmonte, L. M., Sanz-Cánovas, J., García De Lucas, M. D., Ricci, M., Avilés-Bueno, B., Cobos-Palacios, L., Pérez-Velasco, M. A., López-Sampalo, A., Bernal-López, M. R., Jansen-Chaparro, S., Miramontes-González, J. P., & Gómez-Huelgas, R. (2022). Efficacy and Safety of Semaglutide for the Management of Obese Patients With Type 2 Diabetes

and Chronic Heart Failure in Real-World Clinical Practice. *Frontiers in Endocrinology*, *13*. https://doi.org/10.3389/fendo.2022.851035

Pi-Sunyer, X., Astrup, A., Fujioka, K., Greenway, F., Halpern, A., Krempf, M., Lau, D. C., le Roux, C. W., Violante Ortiz, R., Jensen, C. B., & Wilding, J. P. (2015). A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *New England Journal of Medicine*, *373*(1), 11–22. https://doi.org/10.1056/nejmoa1411892

Shah, M., & Vella, A. (2014). Effects of GLP-1 on appetite and weight. *Reviews in Endocrine & Metabolic Disorders*, *15*(3), 181–187. https://doi.org/10.1007/s11154-014-9289-5

Rubino, D., Abrahamsson, N., Davies, M., Hesse, D., Greenway, F. L., Jensen, C., Lingvay, I., Mosenzon, O., Rosenstock, J., Rubio, M. A., Rudofsky, G., Tadayon, S., Wadden, T. A., Dicker, D., Friberg, M., Sjödin, A., Dicker, D., Segal, G., Mosenzon, O., . . . Warren, M. L. (2021). Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity. *JAMA*, *325*(14), 1414. https://doi.org/10.1001/jama.2021.3224

Rubino, D. M., Greenway, F. L., Khalid, U., O'Neil, P. M., Rosenstock, J., Sørrig, R., Wadden, T. A., Wizert, A., Garvey, W. T., Arauz-Pacheco, C., Cannon, K., Downey, H. J., Fitz-Patrick, D., Geohas, J., Gerety, G., Gilbert, J., Hollander, P., Klein, E., Laufer, K., . . . Toth, P. (2022). Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes. *JAMA*, *327*(2), 138. https://doi.org/10.1001/jama.2021.23619

Wadden, T. A., Tronieri, J. S., Sugimoto, D., Lund, M. T., Auerbach, P., Jensen, C., & Rubino, D. (2020). Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in

Primary Care: The SCALE IBT Randomized Controlled Trial. *Obesity*, *28*(3), 529–536. https://doi.org/10.1002/oby.22726

Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *The New England Journal of Medicine*. 2021;384(11). Doi:10.1056/NEJMoa2032183

World Health Organization. (2022). *Obesity*. World Health Organization. https://www.who.int/health-topics/obesity#tab=tab_1