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Semaglutide and Other Interventions for Obesity: A Review of Literature

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Abstract
This study aims to examine the current state of the literature on the use of Semaglutide for weight loss in overweight and obese individuals. While the literature consistently demonstrates that Semaglutide utilization leads to greater weight loss than comparable interventions, questions remain about long term side effects, long term efficacy, affordability, safety, and efficacy in diverse populations. Financial barriers, racial disparities, and comorbid type II diabetes mellitus are factors that influence the research body to continually misconstrue the efficacy, safety, and uses of Semaglutide, highlighting the need for careful academic and clinical analysis of whether Semaglutide is an appropriate prescription for any individual patient. For the purposes of this study, overweight and obese populations are defined according to the standards of the International Obesity Taskforce (IOTF) and the World Health Organization (WHO). Our sample includes the patients who successfully completed landmark trials in nations with diverse research studies on the safety, efficacy, and affordability of products containing Semaglutide, most notably participants in the SUSTAIN and PIONEER trials. This study seeks to explore areas for future research, notable research gaps, biases in the literature, and the apparent differences between sample study participants and those patients being prescribed Semaglutide in various nations and racial groups.

I. Background Information on Obesity Factors

According to the World Health Organization (WHO), obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) over 25 is considered overweight, and a BMI over 30 is obese (World Health Organization, 2019). Given the chronic diseases and conditions associated with obesity (i.e., diabetes, high blood pressure, and heart disease), prevention has been proven to be the best intervention. Current research states that global rates of obesity continue to rise in both children and adults. From 1975 to 2016, the prevalence of obese children and adolescents aged 5–19 years alone increased more than four-fold, from 4% to 18% (Di Cesare et al., 2019). Such statistics are concerning when considering that the likelihood of childhood obesity persisting into adulthood increases as the child ages.

The choice and subsequent analysis of non-pharmaceutical interventions are based on the fact that weight gain is partly caused by elevated energy intake, which often includes a disproportionate amount of refined carbohydrates and/or processed foods (increasing insulin release and fat storage), as well as decreased physical activity (Wilfley et al., 2018). Non-pharmaceutical interventions primarily entail choosing healthier foods (often including fruits, whole grains, and vegetables); limiting unhealthy foods and beverages (often considered refined grains, sugars, greasy foods and more); and limiting sedentary behavior by increasing daily amounts of moderate exercise (at least 30 minutes of moderate physical activity every day) (Wilfley et al., 2018). While some studies such as the 2021 meta-analysis conducted by Daneshzad et el., may report a non-significant association between red meat intake and obesity, the National Institute of Health finds that all meat (red meat, poultry, and seafood) increased the likelihood for obesity by 27%, and by 33% in the development of central obesity. However, the association between red meat and central obesity was weaker than of poultry & seafood and central obesity (19% vs 33%) (Wang & Beydoun, 2009). This finding is further supported by a recent study from the School of Nutritional Sciences and Dietetics at Tehran University that found a diet high in red, white, and processed meats can contribute to weight gain and body fat accumulation, which induces the obesity-related inflammatory process (Shiraseb et al., 2022).

Contrarily, pharmaceutical interventions for weight loss commonly include medications such as Semaglutide, Phentermine-Topiramate, and

Liraglutide. For the purpose of this literature review, we will be reviewing the recent desire for the use of Semaglutide to help with weight loss. Currently, the use of Semaglutide (Wegovy) is supported by its mechanism of action in which it mimics a natural biological hormone called Glucagon-Like Peptide-1 (GLP-1) in areas of the brain that regulate food intake and appetite. Its imitative effects on the patient's brain and digestive system increase satiety, decrease appetite, and reduce cravings in order to lose weight (novoMEDLINK, 2022). It belongs to a class of medications known as glucagon-like peptide-1 (GLP-1) receptor agonists. This class is unique among diabetic medications, insofar as it mimics the effects of the natural incretin hormone produced in the body, helping to lower blood sugar levels and increase weight loss.

Overall Risks and Benefits

A recent meta-analysis found that subcutaneous Semaglutide is currently one of the most effective therapies for weight loss and glycemic control, although it is also commonly associated with gastrointestinal side effects (Hu et al., 2023). Furthermore, studies on efficacy and tolerability have consistently found Semaglutide treatment to be widely effective in populations with type 2 diabetes mellitus with minimal adverse events (Hu et al., 2023). The meta-analysis portion considered the results of 17 randomized clinical trials on 14,940 patients with diabetes mellitus, concluding that Semaglutide use led to significant improvements in HbA1c, body weight reduction, and blood pressure in comparison to placebo. Additionally, compared to placebo and other comparable treatments, Semaglutide demonstrated a tolerable safety profile: it did not increase the incidence of adverse events such as hypoglycemia, acute pancreatitis, or diabetic retinopathy. However, compared to placebo and active comparators, Semaglutide was linked to an increase in nausea, diarrhea, and vomiting (Hu et al., 2023).

However, regardless of Semaglutide's efficacy in appropriate populations, there is always a concern for abuse and misuse of Semaglutide which could lead to adverse events. Chiappini et al. (2023) conducted a review of the FDA's Adverse Events Reporting System (FAERS) to compare the incidence and type of adverse event reports (AERs) linked to Semaglutide against those linked to other weight loss medications. The study found that most AERs were gastrointestinal for GLP-1 analogues such as Semaglutide. It also found an increased rate of reported AERs for Semaglutide compared to other weight-loss drugs, which could possibly be attributed to its popularity, its inherent risks, and/or misuse or off-label use of the drug. Additionally, although the increased proportional reporting rate of Semaglutide is concerning, Chiappini et al. (2023) note that that adverse effects linked to a molecule in the FAERS database do not necessarily demonstrate causation, as the adverse effects could be due to a combination of factors such as comorbidities, dosages, routes of administration, and concomitant drug use. Nevertheless, the study lends credibility to the popular claim that Semaglutide is being abused or misused by those who are not obese or who do not have a prescription (Chiappini et al., 2023).

A fuller understanding of the full range of risks and benefits will require deeper and broader research on diverse populations. The prevalence of strong opinions on Semaglutide in the medical, scientific, and political circles may discourage some providers from habitually or even initially prescribing a controversial drug to their patients. This may be creating clinical data that underrepresents the drug's efficacy in Semaglutide-naïve, appropriate patients, including those who are overweight, obese, diabetic, prediabetic. The other risks and benefits of Semaglutide can be further studied in patients who have an eating disorder, who are overeating as part of depression, or who would benefit from a PRN rapid-acting form while fasting for surgery or lab work. Future retrospective research could examine other health benefits/harms, prevalence of side effects, personalized dosage (i.e., precision medicine using demographic profile, genetic makeup, health history, etc.) and isolate the risk factors for intolerance or non-efficacy. In turn, future prospective research should include large enough samples to start establishing baseline data for a patient population in which the use of prescription and over-the-counter weight loss medication could soon become a realistic recommendation for many or most patients.

Utilization and Benefits of Semaglutide

There are currently only three forms of Semaglutide on the market: Ozempic, Wegovy, and Rybelsus. Ozempic and Wegovy come as an injectable form of Semaglutide. Rybelsus is a newer form of Semaglutide and it comes in pill form. Ozempic comes in three dosage sizes 0.5 mg, 1.0 mg, and 2.0 mg. Wegovy comes in 0.25 mg, 0.50 mg, 1.0 mg, 1.7 mg, and 2.4 mg. Rybelsus comes in two dosage sizes, 7 mg, and 14 mg. Two landmark trials were conducted in January 2017, named SUSTAIN (injectable form of Semaglutide) and PIONEER (oral form of Semaglutide). In these studies, it was found that either form of Semaglutide was more effective than other GLP-1RA drugs (e.g., sitagliptin, liraglutide) for weight loss (Meier, 2021). SUSTAIN saw an HbA1c reduction of about 1.5–1.8% after 30–56 weeks, while PIONEER saw an HbA1c reduction of about 1.0% after 30–56 weeks. Both forms of Semaglutide were also shown to produce significantly more weight loss reduction than other medical forms of weight loss. Semaglutide injections were found to be a little more effective overall than the oral form. According to Rubino et al. (2021), while both forms of Semaglutide are effective for weight reduction, the choice between them ultimately depends on the patient's preference and comfort level.

Adverse Effects of Semaglutide

Semaglutide is used to treat type 2 diabetes by mimicking the action of the hormone GLP-1, which helps regulate blood sugar levels. Although this medication is effective in managing diabetes, there are several adverse effects associated with it. The noted adverse effects that have been found with Semaglutide include diabetic retinopathy, thyroid cancer, injection-site reactions, increased heart rate, acute kidney injury, and gastrointestinal hypo-motility. The risk of hypoglycemia is low in subcutaneous and oral formulations of Semaglutide but is increased when combined with injectable insulin analogues. The mechanisms of gastrointestinal related nausea, vomiting, and diarrhea are not completely understood. The link between Semaglutide and increased risk of thyroid tumors is not fully understood. In addition, patients may experience hypersensitivity reactions that present in the form of itching, rashes, or difficulty breathing. Research has also found that using a medication that mimics a GLP-1 receptor can result in acute kidney injury. Lastly, Semaglutide may worsen patients that have or have had pancreatitis (Smits et. al, 2021).

Semaglutide Use in Other Countries

In 2021, Semaglutide was approved by the Food and Drug Administration (FDA) as an adjunct to reduced calorie intake and increased physical activity for chronic weight management in adults with obesity (initial BMI≥30 kg/m2) or overweight (initial BMI≥27 kg/m2) with at least one weight-related comorbidity. After this, the European Medicine Agency (EMA) granted approval for the use of Semaglutide in Obesity management. Research by Rubino et al. (2021) studied the effectiveness of continued weekly subcutaneous Semaglutide versus a Placebo on weight loss maintenance in adults with overweight or obesity, a randomized, double-blind clinical trial. The sample consisted of 902 participants received once-weekly subcutaneous Semaglutide for 20 weeks, after which 803 participants that were consistent with no missed doses and reached the 2.4-mg/wk Semaglutide maintenance dose were randomized (2:1) to 48 weeks of continued subcutaneous Semaglutide (n = 535) or switched to placebo (n = 268), plus lifestyle intervention in both groups (figure 1).

Effect of Semaglutide 2.4 mg once weekly compared with Placebo on Efficacy Outcomes.

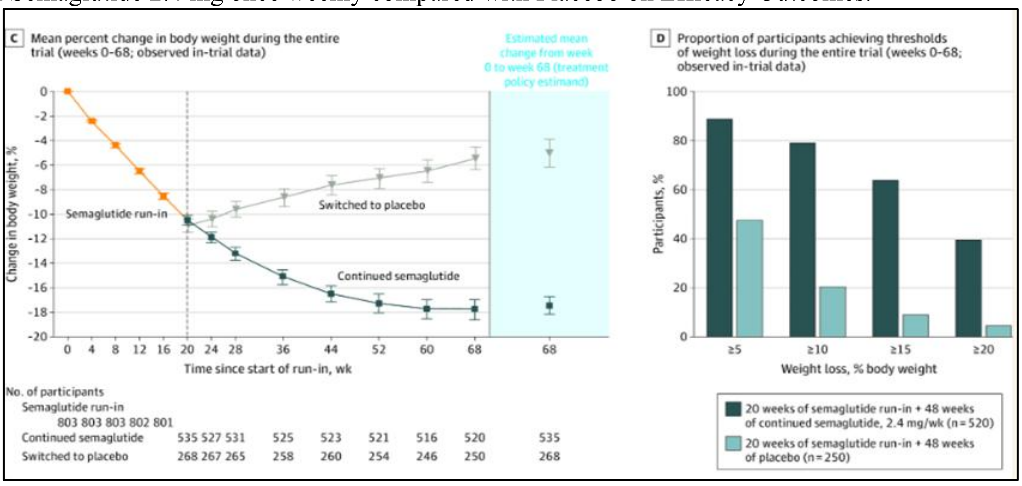

Figure 1

Figure note: The research used in demonstration of this figure (Rubino et al., 2021) seeks to highlight the effectiveness of continued weekly subcutaneous injections of Semaglutide versus a Placebo for weight loss maintenance in overweight or obese individuals. Results shown highlight the significant difference found with the continued use of Semaglutide maintenance dose for 48 weeks over the Placebo with lifestyle interventions.

The study proved that after 20 weeks, when randomization was selected, patients who continued on Semaglutide showed a significant reduction in body weight compared to participants who were switched to a placebo. The weight loss associated with Semaglutide is largely attributed not only to its mechanism of action but also to its capacity to decelerate gastric emptying, thereby diminishing the pace at which nutrients are absorbed in the digestive system. Furthermore, these medications have demonstrated cardiovascular benefits, potentially reducing the risk of heart-related complications in individuals with type 2 diabetes. The use of Semaglutide essentially became global after it was discovered for its magnificent weight loss properties. This popularity skyrocketed after it was given FDA and EMA approval for weight loss management. Today, the drug is prevalent in the United States both as diabetes type 2 medication and for weight loss management. This drug is also popular in Europe, specifically in countries like France, Germany, Spain, Italy, and the UK. However, access to this medication is still primarily driven by cost, which is why it is still limited in developing countries. Currently, in the United States, most insurance companies will only cover the cost of Semaglutide (table 1) when it is used for Diabetes Mellitus type 2, consequently leaving the price "out of pocket" about $804 per month. Additionally, in a National Health and Nutrition Examination Survey 2015 to 2020, Lu et al. (2022) found that the percentage of adults eligible for Semaglutide was highest among Black adults at 56% followed by Hispanic adults. When comparing this data to that of White individuals, it showed that Black and Hispanic individuals were much more likely to be uninsured, lack regular healthcare, or have low family income, presenting yet another significant hurdle for minorities. Therefore, despite meeting the criteria for Semaglutide, participants likely lacked the financial means to afford the medication. This introduces financial barriers along with considerations of race and pricing, as limitations to this medication.

Table 1

List prices of drugs used for weight loss in the U.S. and peer nations

	Ozempic (semaglutide, injection)	Rybelsus (semalglutide, tablets)	Wegovy (semaglutide, injection)	Mounjaro (tirzepatide, injection)
U.S.	$936	$936	$1,349	$1,023
Japan	$169	$69	-	$319
Canada	$147	$158	-	-
Switzerland	$144	$147	-	-
Germany	$103	-	$328	-
Netherlands	$103	$203	$296	$444
Sweden	$96	$103	-	-
United Kingdom	$93	-	-	-
Australia	$87	-	-	-
France	$83	-	-	-

Note: List prices in $USD based on web searches as of August 15, 2023. Prices are for one-month supply of Ozempic 1mg, Rybelus 7mg, Wegovy 2.4mg, and Mounjaro 15mg. Some drugs are not available in all countries and prices were unable to be found in other countries. Some drugs are approved for diabetes and prescribed off-label for weight loss.

Table note: This table seeks to demonstrate how access to Semaglutide is primarily driven by cost, limiting its access in developing countries. Additionally, it is to be noted that the cost of Semaglutide even after insurance coverage in the United States is significant, introducing financial barriers as a limitation to this medication. Source: [KFF analysis of country](#)

II. Methods

Over the past several decades, there has been a global effort to provide reliable and detailed research on the worldwide epidemic of excess weight in children, adolescents, and adults. Our literature review aims to provide a comprehensive description of this work at the national and global level based on the most up-to-date information available, with a specific focus on the role of Semaglutide. This is done in the style of a holistic review of diverse, international research studies, with the intent of exploring, compiling, describing, and evaluating the major findings of rigorous scientific research on Semaglutide. It is imperative that the known facts and scientifically rigorous theories about Semaglutide become widely accessible and well-known not only

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for researchers, but for clinicians, policymakers, payors, public health organizations, and the public at large. High quality research is often lost in the noise of highly biased or unproven claims that are widely circulating in mainstream journalism, social media, and unfortunately even in clinical settings. In order to present a fuller picture of the most rigorous evidence-based medicine, we have included studies producing diverse data sets analyzed and supported by the United Nations Children's Fund (UNICEF), World Health Organization (WHO), World Bank Joint Child Malnutrition Estimates, the Institute for Health Metrics and Evaluation (IHME), Global Burden of Disease Study, and the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).

To analyze the relationship of Semaglutide to obesity, we include two definitions of obesity: the definitions of the International Obesity Taskforce (IOTF) and the WHO growth reference curve. According to the IOTF, obesity is defined as a body mass index (BMI) between 25 and 30 kg/m^2 for persons over age 18 (International Obesity Task Force, 2018). Estimates published by IHME use the IOTF definition. According to WHO, obesity is conceptually defined as abnormal or excessive fat accumulation that presents a risk to health; it is operationally defined such that body mass index (BMI) over 25 is considered overweight, and a BMI over 30 is obese (World Health Organization, 2019). Research and estimates published by UNICEF, WHO, World Bank, and NCD-RisC use the WHO growth reference definition. For this literature review, the classification of obesity will be determined by the definition used in the respective publication, as long the definition is identical to those expressed by either the WHO or the IOTF. Furthermore, the inclusion criteria for our literature review include: 1) Obese as determined by the WHO or IOTF standards, 2) With or without a Diagnosis of DM2.

Inclusion criteria for the SUSTAIN and PIONEER studies were age ≥18 years, a diagnosis of T2D at least 90 days prior to screening, and inadequate glycemic control within a specified HbA1c range (7.0 – 10.0%). In both study trials, initial dose escalation of Semaglutide was implemented to mitigate adverse gastrointestinal events.

During the SUSTAIN study, the efficacy of once-weekly subcutaneous Semaglutide was evaluated in over 7,000 patients in six global phase IIIa trials, and in nearly 3,000 patients in four phase IIIb trials. Oral Semaglutide was then investigated in eight global PIONEER phase IIIa trials in over 8,000 patients, with similarly broad evaluation in different patient populations. Both formulations of Semaglutide were investigated through comprehensive international clinical development programs to minimize differences of formulative therapeutic effects. However, diverse populations may not be adequately represented by such studies, due to the remaining significant differences between qualifying clinical populations and landmark research samples. Therefore, our research also aims to study and assess the influence of financial barriers and racial disparities on the accessibility of Semaglutide for weight management of overweight (BMI ≥27 kg/m2) or obesity (BMI ≥30 kg/m2).

In addition to the landmark SUSTAIN and PIONEER trials, we also considered research by Rubino et al. (2021), in order to analyze the efficacy and safety of Semaglutide in a sample more closely aligned to the diversity of international populations. Following the approval of Semaglutide as an off-label medication for weight management, a randomized double-blind clinical trial known as STEP 4 (Rubino et al., 2021) sampled 902 participants with obesity or overweight with related health issues, including patients from 73 sites in 10 separate countries. Participants initially received Semaglutide injections, with some later randomized to continue or switch to a placebo for 48 weeks. All participants received lifestyle counseling and were monitored to avoid any complications from which data and results were collected. Statistical analyses conducted were recorded using SAS software. The study adhered to ethical guidelines and obtained informed consent from participants.

Furthermore, this study outlines the demographic characteristics of the study population and assesses the proportion of individuals eligible for Semaglutide, as well as examines the association between race, income, insurance status, and access to Semaglutide while acknowledging any factors that are beyond control. Factors such as disparities in access driven by cost. Additionally, it investigates insurance coverage limitations in the U.S. Retrospectively, it analyzes data from the National Health and Nutrition Examination Survey, exploring racial disparities in eligibility and affordability as critical limitations to Semaglutide accessibility (Lu et al., 2022).

We find that our biases include disregard for the potential effects of other comorbidities including but not limited to diabetes mellitus; this itself is an indication for the use of Semaglutide. In turn, this would complicate a systematic review focused on the use of Semaglutide specifically for weight loss. We found that excluding specific comorbidities, demographics, or treatment indications from our study would prevent consideration of the largest and most significant studies performed so far in the brief history of Semaglutide's use in nondiabetics. Therefore, a more holistic approach to all landmark studies allows meaningful analysis of weight loss in realistic clinical populations. In the future, post-marketing trials could continue to lend more insight into these clinical populations.

Additionally, weight loss can improve multiple health outcomes in patients with or without diabetes. Therefore, although comorbidities could significantly affect the efficacy of Semaglutide, our intent is to focus broadly on obese populations. Another research limitation is that we are not considering patients using Semaglutide who are not obese. With the burgeoning use of Semaglutide in many overweight, normal weight, or even underweight patients (with or without the approval of their medical providers), future research should compare patients in all BMI categories. Not only might weight change differ between patients of different BMIs, but side effect profiles could differ greatly as well, with rising concern about normal or underweight patients using Semaglutide off label, with inappropriate prescription, or without a prescription.

III. Results

Interventions for Obesity

When it comes to individuals who are currently obese, integrated care for complex behavioral health problems becomes more common and great efforts must be used in clinical interventions. With a primary focus on the findings from a study from UCLA Health 2023 that used tailored behavioral therapies and Semaglutide, results showed that after 68 weeks, nearly a third of the adults using Semaglutide lost 20% of their body weight; whereas adults who only incorporated diet and lifestyle modifications only lost about 2% of their weight. Additionally, it was noted that after one year of Semaglutide and lifestyle intervention cessation, participants regained two-thirds of their pre-intervention body mass (Wilding et al., 2022). In a clinical trial by Rubino et al. (2021) that enrolled 803 predominantly white and female participants, continuous Semaglutide treatment exhibited robust efficacy. Participants experienced a mean weight reduction of −7.9% from week 20 to week 68, contrasting sharply with a +6.9% weight gain observed in those switched to placebo (fig 1). This significant difference underscores Semaglutide's capacity not only to promote weight loss but also to improve metabolic health markers, including substantial reductions in waist circumference (−9.7 cm) and BMI (−4.7) compared to placebo.

The statistical finding of the UCLA Health 68-week study can be generalized across 78% of the studies (n =4,154) analyzed in our systematic review on the use of Semaglutide for weight loss. These findings confirm that the chronicity of obesity requires ongoing treatment and lifestyle modifications to maintain improvements in health and weight. For the 22% of studies that did not report similar findings, continuous monitorization of weight loss was not progressively reported throughout the duration of the study for a majority of participants, rendering the study's data insufficient or insignificant. Additionally, another limitation of these studies is the number of patients that withdrew from study, most often as a result of intolerable gastrointestinal side effects.

Eligibility for Semaglutide

Data analysis from the National Health and Nutrition Examination Survey (NHANES) conducted by Lu et al. (2022) between 2015 and 2020 discovered that a total of 13,711 adults met the eligibility criteria for Semaglutide, representing approximately 51.1% of the US adult population, approximately 112.5 million adults. The mean age of eligible adults was 50.6 years. Significant variations in eligibility were observed across racial and ethnic groups, with the highest percentages among Black adults at 56.6%, Hispanic adults at 55.0%, White adults at 50.5%, and lower among Asian adults at 19.8%. However, it is important to note that eligibility doesn't equate to getting correct and consistent treatment, not least of all between American demographics, so in any analysis of the early research on Semaglutide in weight loss on Americans, it is important to note other factors (including Social Determinants of Health) should be considered in how data should be analyzed, weighed, and compared to the actual population.

Additionally, analysis from the National Health and Nutrition Examination Survey (NHANES) reveals significant disparities in Semaglutide eligibility across racial and ethnic groups. While approximately 51.1% of the US adult population meets eligibility criteria, access barriers persist due to socioeconomic factors. Hispanic, Black, and Asian populations are disproportionately affected, with higher percentages experiencing lack of healthcare access, low income, lower educational attainment, and unemployment (Lu et al., 2022).

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Socioeconomic and Demographic Factors

Financial barriers and social determinants of health significantly influenced eligibility and access to Semaglutide among different racial and ethnic groups. According to Lu et al. (2022), of all eligible patients for Semaglutide, a total of 13.3% lacked a usual source of care, 33.6% had low family income, 38.9% lacked higher education, 35.0% were unmarried, 37.0% were unemployed or not in the labor force. The percentage of uninsured adults who lacked a usual source of care, had low family income, or lacked higher education was consistently highest among Hispanic adults, followed by Black adults, Asian adults, and then White Adults (Lu et al., 2022).

Overall Risks and Benefits Associated with the Utilization of Semaglutide

To summarize the risks and benefits associated with the use of Semaglutide, our research finds that despite gastrointestinal side effects in some patients and unknown long-term safety/efficacy, Semaglutide appears to be one of the most effective therapies for weight loss. Additionally, the use of different brands and administration routes of GLP-1 receptor agonists are equally effective for weight loss and reduction of A1C. Although physical activity and non-GLP-1 weight loss medications such as Orlistat and Phentermine can aid in weight management, GLP-1 receptor agonists like Semaglutide have demonstrated superior efficacy in weight loss and metabolic health outcomes, as evidenced by the substantial outcomes reported in the study by Rubino et al. (2021). One important exception is that the oral form of Semaglutide (currently available as Rybelsus) may be slightly less effective for weight loss than other forms, though it was equally effective for A1C reduction in patients with Type 2 Diabetes Mellitus.

Adverse Effects of Semaglutide

To summarize our findings on the overall risks and benefits of Semaglutide use, the literature shows that it is one of the most effective approaches for weight loss available today; however, concerns remain around known side effects, unknown long-term effects, and permanence of weight loss. The largest meta-analyses so far have consistently shown efficacy of the drug relative to placebo and other diabetic medications for weight loss (Hu et al., 2023). However, severe gastrointestinal side effects have been reported anecdotally, requiring further study: adverse event reports are higher for Semaglutide than for other weight loss drugs, which could reflect a danger on the one hand, or a sign of the popularity of the drug on the other hand (Chiappini et al., 2023). Given this data, the adverse effects of Semaglutide should be considered before being authorized for patients.

IV. Discussion

Obesity is a significant public health problem affecting all ages groups, primarily children and adolescents aged 5–19 years, and is associated with serious physical comorbidities that cause distress and impairment. Behavioral interventions such as choosing healthier foods, limiting unhealthy foods and beverages, and limiting sedentary behavior are the cornerstone in preventing obesity and are effective for many when it comes to losing weight. It has been recognized that the key drivers, particularly when aimed at younger ages for prevention of adult obesity, includes changes to food systems and implementation of effective programs and policies in multiple sectors to address overnutrition, undernutrition, mobility, and physical activity (Wilfley et al., 2018), with these issues addressed both locally and globally.

This review considers the landmark trials (SUSTAIN and PIONEER) on Semaglutide in order to expand the scope of future research into pressing topics such as the ways and routes by which Semaglutide can be used, against changes in variables such as weight or diabetic health. We also considered the role of other major studies highlighting the research gaps around Semaglutide in diverse populations that may not be adequately represented by early landmark trials. Our research finds that despite gastrointestinal side effects in some patients and unknown long-term safety/efficacy, Semaglutide appears to be one of the most effective therapies for weight loss. Additionally, different types, formulations, and administration routes of GLP-1 receptor agonists were generally found superior to other medication classes for weight loss and reduction of A1C. Although physical activity and non-GLP-1 weight loss medications such as Orlistat and Phentermine can aid in weight management, GLP-1 receptor agonists like Semaglutide have demonstrated superior efficacy in weight loss and metabolic health outcomes, as evidenced by the substantial outcomes reported in the study by Rubino et al. (2021). Furthermore, Semaglutide has been found more effective for weight loss than other GLP-1RA drugs (Meier, 2021). One important exception is that the oral form of Semaglutide (currently available as Rybelsus) may be slightly less effective for weight loss than other forms of Semaglutide, though it was equally effective for A1C reduction in patients with Type 2 Diabetes Mellitus (Rubino et al., 2021).

Furthermore, the statistical finding across the majority of our studies (78%) in using Semaglutide for weight loss, for a duration ≥20 weeks, confirms that the chronicity of obesity requires ongoing treatment and lifestyle modifications to maintain improvements in health and weight. Researchers at the National Institute of Health Research aimed to explore the changes in body weight and cardiometabolic risk factors after the cessation of Semaglutide and lifestyle intervention for weight loss. Researchers found that after one year of Semaglutide and lifestyle intervention cessation, majority of study participants regained two-thirds of their pre-intervention body mass, with similar changes in cardiometabolic variables. This finding highlights the need for a dietary and physical intervention encompassed with the use of Semaglutide for obese adults who aim to achieve a 20% or more reduction in body weight. This finding reported across the majority of our studies confirms that the chronicity of obesity requires ongoing treatment in addition to lifestyle modifications, such as a reduction in caloric intake and an increase in physical activity, to maintain improvements in health and weight (Wilding et al., 2022).

For studies that did not report similar findings, continuous monitorization of weight loss was not progressively reported throughout the duration of the study for a majority of participants, rendering the study's data insufficient or insignificant. Additionally, analysis of these studies must account for other limitations, such as participants that withdrew from study due to intolerable gastrointestinal side effects.

V. Conclusion

Future research can explore the many remaining research gaps on the use of Semaglutide for weight loss. Close consideration of socioeconomic factors such as accessibility to health care, nationality, racial disparities, and income must occur in future research on the effects of Semaglutide, as many demographics are left unconsidered or underemphasized by the current research body. Additionally, the majority of research presents the effects of Semaglutide in patients with Type II Diabetes Mellitus, but the effects of this medication on patients with Type I Diabetes Mellitus needs to be further studied and represented as well. Furthermore, a majority of the studies we've reviewed failed to reveal the percentage breakdown of different co-morbidities in their respective cohorts. This information is valuable and can bring insight on potential risks between certain comorbid conditions and administration of Semaglutide. Collection or publication of this data from original landmark trial participants would allow further longitudinal research. This approach would help address the ongoing major gaps in the research, especially in regard to long term efficacy for weight loss, improvement in comorbidities, and side effects.

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