GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Basic Medical Science—Master of Science

2024

ABSTRACT

This paper aims to provide a detailed exploration of the development of glucagon-like peptide receptor (GLP-1) agonists along with their uses, effects, and societal impact. As this class of medications has progressed from the 1980s to the current day, multiple FDA-approved medications have been produced. These medications have both beneficial and negative side effects on multiple organs in the human body. The differences between glucagon-like peptide receptor agonists include the length of half-life, effectiveness in weight loss and glycemic control, the intensity of side effects, and the specific incretin hormones stimulated. Semaglutide was proven to induce statistically significant increased weight loss compared to placebo in multiple clinical trials. There are clear disparities in obesity and Type II diabetes outcomes, acquiring proper medication, and affordability based on socioeconomic status and race. Pharmaceutical compounding has resulted because of the high demand for glucagon-like peptide receptor agonists and the inability of those of low socioeconomic status to pay for these drugs in cash because these drugs are often not covered for weight loss by insurance. In conclusion, the efficacy of glucagon-like peptide receptor agonists has been ground-breaking, and going forward, these medications need to be accessible to those who need them most regardless of socioeconomic status.

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INTRODUCTION

The obesity epidemic in the United States has continued to grow and shows no indication of slowing down. Alongside this epidemic, healthcare costs are also on the rise, making it more difficult to combat obesity. Healthcare is not only expensive but also seemingly exclusive. Lack of access is more prevalent in communities of lower socioeconomic status. Those communities are more heavily affected by comorbid conditions like obesity and diabetes. There have been recent developments in both injectable and oral treatments for these conditions. The value of these drugs is immense due to the previous lack of reliable, effective pharmaceutical solutions and the current prevalence of diabetes and obesity. One of these recent pharmacological solutions is the glucagon-like peptide 1 receptor agonists (GLP-1). Decades of research and testing, initially with mice and then with humans have shown very promising results. These drugs were initially created for diabetes treatment but many clinical trials have shown positive, substantial effects for weight loss and other conditions. Along with proper diet and exercise, these drugs can cause weight loss which leads to improvement in diabetes for many patients. The issue with GLP-1 receptor agonists (and other medications) goes back to the cost of these medications, which need to be consistently taken by those in need. With the recent increase in use and growing popularity of these medications, the price has increased from previous ranges. This leaves those with lesser socioeconomic status and little to no health coverage at a disadvantage, and potentially unable to receive the care they need. This paper aims to have a full exploration of GLP-1 receptor agonists development, use, effects, and societal impact among other topics.

HISTORY OF GLP-1 RECEPTOR AGONISTS

A relatively recent avenue to try to reverse the course of the growing worldwide diabetes concern has come with the advent and research on the glucagon-like peptide-1 hormone (GLP1). Incretin hormones are gut peptides secreted after nutrient intake that are further stimulated by hyperglycemia and insulin secretion. These hormones include GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 helps regulate blood sugar levels and suppresses appetite. Taspoglutide was the first GLP-1 receptor agonist to be approved to be used for once weekly dosing but is not currently on the market because of the substantial risks of allergic reactions at the injection site (Knudsen and Lau 2019). A short-acting glucagon-like peptide-1 receptor agonist, exenatide, was first approved in the US in 2005. Liraglutide, the first long-acting GLP-1 receptor agonist to become available for the treatment of type two diabetes, received market authorization in 2009 in the European Union (EU). Semaglutide, another long-acting GLP-1 agonist was FDA approved in 2017. Recently tirzepatide, a dual glucose dependent insulinotropic polypeptide (GIP) and GLP-1 agonist (the first of its kind), was approved in 2022 in the United States of America (U.S.). by the FDA.

Initial evidence of GLP-1 amide binding to receptors in the brain and pancreas was published in the late 1980s. Activation of these receptors was shown to stimulate the adenylate cyclase pathway, increasing cyclic AMP (cAMP) and causing an increase in insulin secretion (Knudsen and Lau 2019). GLP-1 is a peptide hormone with a short half-life. Given the short half-life of the drug, a constantly higher and stable plasma concentration of GLP-1 is needed for therapeutic use (Knudsen and Lau 2019). The most common method of administration of GLP-1 medication is subcutaneous injections.

Multiple common forms of GLP-1 receptor agonists have been researched and tested for their use which include: semaglutide, liraglutide, and tirzepatide (a dual GLP-1/GIP agonist). Liraglutide has the best pharmacokinetic properties for optimum once daily dosing due to differences in amino acids in the N-terminal and fatty chain structure from natural GLP-1 that allow for more albumin-binding, and therefore a longer half-life while maintaining GLP-1 receptor potency (Rubino et. al 2021). Albumin binding is the technique to make the GLP-1 agonists longer lasting. Peptide-based ligands when bound to albumin have been shown to significantly increase the half-life of the peptide-based ligands. Albumin is a natural carrier of various substances throughout the body and has a multitude of binding sites to be a carrier for drugs, which allows for many drug-drug interactions. Studies have revealed that liraglutide also has delayed subcutaneous absorption, important for extending the bioavailability of the peptide hormone (Knudsen and Lau 2019).

Another key property of liraglutide is its partial protection from rapid dipeptidyl peptidase-4 (DPP-4) degradation. This is important to a more lengthened half-life because when incretin hormone GLP-1 is released or administered, DPP-4 usually follows to degrade the hormone and subsequently reduce its effects. Protection from DPP-4 for liraglutide may be due to the reversible binding to albumin, or direct steric hindrance (Knudsen and Lau 2019). Some diabetes medications, like sitagliptin, specifically inhibit DPP-4. Another way to combat the short halflife of GLP-1 receptor agonists is to create a sustained release formulation. This idea led to the approval of the injectable encapsulated formulation of exenatide: exenatide extended release (Knudsen and Lau 2019). The oral form of exenatide was developed to increase patient compliance.

GLP-1 RECEPTOR AGONISTS AFFECT DIFFERENT ORGAN SYSTEMS

The organ systems in the human body are all interconnected. This is why the effects drugs have on each system must constantly be monitored during their development. During the creation of medication for diabetes, the organs primarily affected or targets will likely be organs in the foregut because the foregut contains organs that affect blood glucose levels. The foregut includes the pancreas, the organ that releases insulin and glucagon. GLUT 4 receptors in muscles could also be targeted. The connection between the pancreas, the gut, and incretin hormones was discovered in the early part of the twentieth century (Knudsen and Lau 2019) That connection has been heavily studied and manipulated to try to improve the health outcomes of those affected with diabetes. The pancreas is the main target organ for the action of GLP-1 receptor agonists in diabetes treatment because the pancreas produces insulin and glucagon which are two key innate factors that affect blood glucose levels. Functional effects in the pancreas include the glucose dependent release of insulin, and the upregulation of the biosynthesis of insulin, glucokinase, and glucose transporters. This explains why GLP-1 receptor agonists' relationship with weight loss, glucagon, and blood glucose levels has a large effect on insulin sensitivity (Knudsen and Lau 2019). Specifically, among GLP-1 receptor agonists these reductions in insulin resistance were shown to be greater with semaglutide vs. placebo, sitagliptin (a DPP-4 inhibitor), or exenatide extended release (Knudsen and Lau 2019). GLP-1 receptor agonists also induce glucose dependent lowering of glucagon secretion, which lowers glucose output from the liver. In the pancreas, GLP-1 receptors are predominantly on insulin producing beta-cells, with a significantly weaker expression on acinar cells of the exocrine pancreas. This is likely why patients who take GLP-1 receptor agonists have better responses from their beta cells while on the medication (Knudsen and Lau 2019).

Most GLP-1 is produced in the gastrointestinal tract, and GLP-1 receptor expression has been ascribed to the myenteric plexus (responsible for the peristaltic movement of the bowels and connects the central nervous system and the enteric nervous system) neurons throughout the gut (Knudsen and Lau 2019). These neurons are the reason that GLP-1 exerts its important physiological effect of regulating GI motility. With pharmacological administration of GLP-1, this effect on GI motility is subject to rapid but incomplete desensitization (Knudsen and Lau 2019). The highest level of GLP-1 receptor expression in the gut is in the Brunner's glands in the upper duodenum. The upper duodenum is one of the highest GLP-1 receptor expressing organs in humans (Knudsen and Lau 2019). A function of Brunner's glands is to secrete mucus to lubricate the intestinal wall and GLP-1 can act on these glands to increase mucus secretion, thereby decreasing inflammation and protecting against intestinal damage.

The GLP-1 receptor is also localized to the myocytes of the sinoatrial (SA) node in the heart. This may be the reason GLP-1 receptor agonists demonstrate numerous cardiovascular protective effects. These effects can happen in subjects with or without diabetes. Several cardiovascular outcomes trials involving GLP-1 receptor agonists have supported the overall cardiovascular benefits of these drugs, which include: lower plasma lipid levels and lower blood pressure (BP), both of which contribute to a reduction of atherosclerosis and reduced coronary vascular disease (Ma et. al 2021).

GLP-1 receptor agonists also have effects on the central nervous system outside of the connection with the myenteric plexus. Exenatide acts more like endogenous GLP-1 and communicates to the brain primarily via the Vagus nerve, while liraglutide and semaglutide access the brain directly (Knudsen and Lau 2019). GLP-1 receptors in the brain may be involved in reward-related feeding behavior. A study with semaglutide in patients with obesity did indicate

a change in food preference and a positive effect on reward (Knudsen and Lau 2019). This means GLP-1 receptor agonists not only can help patients combat diabetes and obesity through its effects but can potentially change their behavior to have healthier habits. GLP-1 receptors in the brain have been described as being involved in, but not essential for, memory and learning. Furthermore, GLP-1 receptor agonists have been associated with anti-inflammatory, neurotrophic, and neuroprotective properties in neurodegenerative disorder preclinical models, and hold promise for repurposing as a treatment for neurodegenerative diseases (Kopp et. al 2022). This means current FDA approved GLP-1 receptor agonists for the treatment of neurodegenerative diseases may be a reasonable off-label use as an additive to neurodegenerative diseases such as Alzheimer's or Parkinson's treatment plan because of the medications lessening of neuroinflammation (Kopp et. al 2022). In countries all over the world, the obesity pandemic is present regardless of GDP. Based on its prevalence, this creates an urgency to combat rising obesity and diabetes with modern solutions that have high efficacy and affordability. The purpose of GLP -1 receptor agonists is to help with glycemic control in people with Type 2 Diabetes. Long-acting GLP-1 receptor agonists (liraglutide and semaglutide) not only increase glycemic control, but reduce body weight, and reduce cardiovascular risk. Also, GLP-1 receptor agonists demonstrated prevention of the onset of macroalbuminuria and reduced the decline of GFR in patients with diabetes (Greco et. al 2019). Significant weight loss, through an effort to reduce energy intake, led to the approval of liraglutide and semaglutide for the treatment of obesity. Other semaglutide uses include the treatment of non-alcoholic fatty liver disease (NASH) (Knudsen and Lau 2019).

DIFFERENCES AMONG GLP-1 RECEPTOR AGONISTS

There has been an evolution of GLP-1 receptor agonist medication. It began with initial research finding a relationship between adenylyl cyclase pathways, G-coupled protein receptors, and their relationship to obesity and diabetes in the late 1980s. Then, there was the development and experimentation of GLP-1 receptor agonists in the early 2000s. Most recently, the FDA approved tirzepatide (a combination of GLP-1 receptor agonist and a gastric inhibitory polypeptide (GIP) agonist) in 2022. Exentide came first in the early 2000s as a short acting GLP-1 receptor agonist, then liraglutide and semaglutide were developed to solve the issue of the short life associated with these drugs. The differences between the short and long acting GLP-1 receptor agonists involve the albumin binding that carries the medication through the bloodstream and prolongs its bioavailability. Semaglutide has been shown through multiple studies to more effectively induce weight loss and have more glycemic control in both patients with and without diabetes compared to liraglutide. The reduction in calorie intake observed with semaglutide is approximately twice that with liraglutide (Knudsen and Lau 2019).

The major difference between these long-acting GLP-1 receptor agonists and tirzepatide is that tirzepatide is also a GIP agonist. Because of this component, tirzepatide stimulates B cell insulin secretion (Rubino et. al 2022). As mentioned earlier, liraglutide and semaglutide also affect insulin sensitivity. Tirzepatide also reduces HbA1c and generates more weight loss than semaglutide in Type 2 diabetic patients.

The most common side effect of the GLP-1 receptor agonists class is GI-related adverse events including nausea, diarrhea, constipation, and vomiting which are dose-dependent and typically present in the up-titration phase (Knudsen and Lau 2019). These side effects occur in the up-titration phase because the up-titration phase is used to evaluate what specific amount of a drug a

patient can tolerate until a maximum effective dose is realized or when negative side effects start to occur. In various clinical trials, it has been shown that most GI adverse effects with GLP-1 receptor agonists are mild and transient but can lead to premature treatment discontinuation in some patients (Knudsen and Lau 2019). Proper dosing through initial titration of both liraglutide and semaglutide dosing should be done to keep GI symptoms mild to maximize the benefits of the drugs (Knudsen and Lau 2019). This is important to an extent because the higher the dose, the more beneficial it can be for patients so finding their highest tolerable dosage is essential to maximize benefits while minimizing side effects. Patients with renal deficiencies do not have to be concerned with renal complications that may necessitate renal-dosing, because neither drug is cleared via the kidney (Knudsen and Lau 2019). Among the more commonly prescribed long acting GLP-1 receptor agonists, semaglutide is more likely to have GI adverse effects than liraglutide (Rubino et. al 2022).

Weight loss is the most popularized effect these medications have. More weight loss and fasting glucose control are observed with long-acting GLP-1 receptor agonists despite the lesser effect of these drugs on gastric emptying than short-acting GLP-1 receptor agonists, like exenatide (Knudsen and Lau 2019). As mentioned previously, when comparing long-acting semaglutide and liraglutide, semaglutide has been proven to be more effective for inducing weight loss and lowering HbA1c. A relevant study included 127 participants who were randomized to receive once-weekly subcutaneous semaglutide, 2.4 mg (maximum dose) with 16-week escalation; or matching placebo, or 127 patients with once-daily subcutaneous liraglutide, 3.0 mg (maximum dose) with 4-week escalation, or matching placebo, plus diet and physical activity (Rubino et. al 2022). The diet and physical activity were most likely added to the experimental intervention because most patients suffering from obesity and/or diabetes would likely have this in their

treatment plan. In the randomized clinical trial the participants mostly were white and female. The participants' mean age was 49 years, mean body weight was 104.5 kg, mean BMI was 37.5, mean waist circumference was 113.3 cm, and 36.1% had prediabetes, per American Diabetes Association criteria. Most had 0 to 2 comorbidities at screening, with dyslipidemia and hypertension being the most prevalent (Rubino et. al 2022). The study lasted longer than a year under these conditions and the results showed a mean body weight change from baseline to 68 weeks was –15.8% with semaglutide vs –6.4% with liraglutide, a statistically significant difference (Rubino et. al 2022). Among overweight or obese adults without diabetes, once weekly subcutaneous semaglutide, compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity resulted in significantly greater weight loss at 68 weeks (Rubino et. al 2022).

The significance of a study like this besides the indications between the GLP-1 receptor agonists semaglutide and liraglutide, is how well the medications worked on patients who are not diagnosed with diabetes. Even though it has been previously discussed the alternative uses of GLP-1 receptor agonists for obesity, the effectiveness of these drugs in a healthier population can be problematic if given to those who aren't specifically in a medical need for it. The societal issues of GLP-1 receptor agonist use in those who aren’t obese or diabetic will be discussed later.

SEMAGLUTIDE FINDINGS IN CLINICAL EXPERIMENTS

A third study for reference has been provided to show the difference between continued semaglutide use in patients versus patients taken off of semaglutide for a while after previously being on it. The importance of this study is to show the most effective use of semaglutide and other GLP-1 receptor agonists. When GLP-1 receptor agonists are used to help patients lose weight and have more glycemic control while they develop healthier overall lifestyle habits such as proper diet and exercise. The drug alone will initially help many lose weight and have other beneficial effects on overall health. However, sustainable results and maintenance of a healthier physical condition need more than just the medications alone. A reversal back to a previous state or worse physical health after stopping a GLP-1 agonist can be seen if certain dietary and behavioral changes aren't made. As it has been supported by previous discussions of GLP-1 receptor agonists on certain organ systems, other measurements such as blood pressure and waist circumference, two commonly used measurements to assess health, were improved in the patients who participated in the study on semaglutide. The setup of the clinical study was also a randomized, double-blind, 68-week phase 3a withdrawal study conducted in 10 countries from June 2018 to March 2020 in adults with a body mass index of at least 30 (or ≥27 with ≥1 weight-related comorbidity) and without diabetes (Rubino et. al 2021). In this study the primary endpoint was the percent change in body weight from week 20 to week 68; confirmatory secondary endpoints were changes in waist circumference, systolic blood pressure, and physical functioning (Rubino et. al 2021). These data points are used to compare participants who continued once-weekly treatment with subcutaneous semaglutide (2.4 mg) for 68 weeks and those who switched to placebo after week 20 (Rubino et. al 2021).

Among adults that met the criteria for being overweight or obese who completed a 20-week use period with subcutaneous semaglutide (2.4 mg once weekly), maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks (Rubino et. al 2021).

It has been thoroughly established that GLP-1 receptor agonists lower appetite and food intake. This means there are possibly other beneficial factors besides those mentioned above. Liraglutide can increase fat oxidation (Knudsen and Lau 2019). Semaglutide can reduce cravings, increase the ability to control food intake, and alter food preferences (prefer lower-fat, healthier foods over foods high in fat) (Knudsen and Lau 2019). This specific reduction in food cravings and altered preference for more nutrient rich foods can be reasoned as to why semaglutide across a multitude of studies results in consistently stronger weight loss effects than liraglutide. Semaglutide partially prevented Western diet-induced changes for transcripts associated with pathways relevant to the pathogenesis of atherosclerosis, and the changes appeared to be independent of the doses used, whereas a typical dose-response relationship was seen for weight loss and triglyceride lowering (Knudsen and Lau 2019).

SOCIOECONOMIC STATUS, RACE, AND DRUG COST

The reductions in food intake and food cravings with semaglutide are very helpful in the long term treatment of those afflicted with obesity and diabetes. However, as multiple studies have shown, these effects are not limited to those with these health conditions. The prospect of a very successful weight loss medication has led to the use of GLP-1 receptor agonists in people without pertinent health concerns. Word of mouth, social media, and constant daily commercials about GLP-1 receptor agonists have made these drugs more present in the current social consciousness. With that increased awareness, celebrities who require the medication and those who do not both use GLP-1 receptor agonists for their weight loss benefits. Celebrities from Oprah Winfrey to comedian Tracy Morgan to trainer Jillian Michaels among others have all voiced their various opinions on Ozempic (semaglutide) and its use in celebrity culture (People.com). What can be said is that whatever means celebrities or those who desperately want semaglutide for its weight loss effects and who may not need the medication are part of the problem with current shortages of the product. They are not the only ones at fault, providers who are writing the prescriptions necessary to make GLP-1 receptor agonists available to those who are not in need are causing an issue for those with lesser access to these medications who are in need. Presumably, most celebrities are of higher socioeconomic status, and because of this, they buy these medications in cash. Abusing this "privilege" has caused a disparity that has led to pharmaceutical compounding.

Healthcare availability and affordability are even more accentuated in those of lower socioeconomic status. Those of lower socioeconomic status are usually minorities, turning drug shortages into not just a class issue but also a racial one. Most people in the United States with diabetes are of non-white ethnicity (Rosenstock et. al 2014). Although there is a difference in the

prevalence of diabetes between whites and minorities in the U.S., racial economic inequality had the greatest impact on the disparity, followed by segregation (Rosenstock et. al 2014). This supports the fact that individual poverty and living in a poor neighborhood increased the odds of having diabetes for both whites and blacks (Gaskin et. al 2014). Even though socioeconomics has the greatest impact, an important nuance is black adults living in a poor neighborhood had similar rates of diabetes regardless of individual poverty status, but non-poor whites were able to mollify the harmful health effects of living in a poor neighborhood (Gaskin et. al 2014). Health outcomes differing by race are further supported by in Baltimore, Maryland, a black man is 50% more likely to die from diabetes than his white counterpart; just 40 miles away in Washington D.C., that same black man is nearly 300% more likely to die from diabetes (Tung et. al 2017). This is not independent of Washington D.C. though, blacks are dying at a higher rate from diabetes than whites in virtually every major city in the nation, and this indicates that the highly populated cities bear a disproportionate burden of this disparity (Rosenstock et. al 2014). The issue with racial health disparities is not limited to obesity, type 2 diabetes, or GLP-1 receptor agonists like semaglutide. Use of an SGLT2 inhibitor treatment increased among patients with type 2 diabetes (because of its cardioprotective benefits) from 2015 to 2019, yet black and female patients and patients with low socioeconomic status were less likely to receive an SGLT2 inhibitor, suggesting that interventions to ensure more equitable use are essential to prevent worsening of well-documented disparities in cardiovascular and kidney outcomes in the US (Eberly et. al 2021).

The economic disparities are that lead to healthcare inequity not limited to the U.S. But the U.S. for the class of drugs discussed in this paper does consistently have the highest prices. This further perpetuates how the cost of healthcare is substantially higher in the U.S. compared to the

rest of the world, furthering the socioeconomic and racial issues with obesity and diabetes in the U.S. Figures 7-10 show comparisons of semaglutide, liraglutide, tirzepatide prices in the U.S. and the rest of the world. Figure 11 shows the price comparison of liraglutide and semaglutide compared to other commonly used drugs in the U.S. for both adults and adolescents.

Drug Price comparison (Levi et. al 2023).

These high monthly prices for people with obesity and diabetes create financial hardships for people who can't afford these medications. Medical insurance may be able to cover the cost, but for people with low or no insurance coverage and overall means, being able to afford these medications is unlikely. This issue isn't an uncommon one and there have been solutions put in place to possibly ease the economic burden people may be having to afford their medications. Pharmacy compounding medicines is necessary when an FDA-approved drug is not available or appropriate for the patient or must be altered in some manner, such as strength or route of delivery (Gudeman et. al 2013). The FDA defines traditional pharmacy compounding as the combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription(Gudeman et. al 2013). It needs to be made clear that compounded drugs are not equivalent to generic drugs. An important difference is that pharmacy compounded products are not clinically tested for safety and efficacy, nor is bioequivalence testing conducted as is required for generic drugs yet these drugs are still approved (Gudeman et. al 2013). The type and extent of quality control testing required for FDA-approved drugs are greater than the testing done on compounded preparations. Compounding pharmacies often rely upon Certificates of Analysis from suppliers rather than retesting incoming bulk ingredients as pharmaceutical manufacturers are required to do by GMPs (Gudeman et. al 2013). Another dissimilarity is that compounding pharmacies are exempt from the federal GMP regulations that are obligatory for all approved pharmaceutical manufacturers (Gudeman et. al 2013). Beyond the unregulated delivery of these drugs, there is not much warning about the safety of these drugs to patients. Unlike the product labeling of FDA-approved drugs, the labeling of compounded preparations is neither federally regulated nor

federally standardized (Gudeman et. al 2013). Thus, compounded medications may be distributed without any federal regulation regarding contraindications to use, warnings, precautions, and drug interactions. Compounded medications do not require the same federal oversight and standards as generic medications. Pharmacological compounding is a way to supply drugs with less FDA oversight on manufacturing and quality control. False advertising is also possible with these medications. Advertising and promotion of approved drugs are subject to FDA oversight and restriction, including a fair balance of safety information as mentioned previously while compounded medications are not (Gudeman et. al 2013). To ensure that patients and healthcare providers are properly informed, it has been proposed that the labeling on compounded preparations should state that they have been approved as safe by the FDA but they are delivered in another form (Gudeman et. al 2013). Another possible safety concern with compounding pharmacies (and all approved drugs) is that adverse events do not have to be reported to the FDA. Thus, adverse events associated with compounded drugs may be difficult to detect, particularly if the affected patients are widely scattered in different geographic areas (Gudeman et. al 2013).

CONCLUSION

GLP-1 receptor agonists have the potential to change the future of diabetes and obesity treatment across the world. The myriad of clinical studies that have diverse, representative populations showing consistent statistically significant positive results for those afflicted with diabetes cannot be disputed. There are also positive and negative side effects that interact with other organ systems as is the case with most medications. Given the extent of the health issue trying to be lessened, advancements with this type of medication should be explored. Proper steps need to be taken to ensure a high quality product that is safe to be used by patients even during periods of shortage where compounding may be necessary. Proficient, affordable GLP-1 receptor agonists need to be made available to those who cannot afford the more expensive options given the current price point even with insurance. Without trying to solve societal systemic inequalities towards minorities, especially those of low socioeconomic status, actions need to be taken so that as many people as possible can get access to this medication if it is a part of the recommended treatment plan.

REFERENCES

Eberly, L. A., Yang, L., Eneanya, N. D., Essien, U., Julien, H., Nathan, A. S., Khatana, S. A. M., Dayoub, E. J., Fanaroff, A. C., Giri, J., Groeneveld, P. W., & Adusumalli, S. (2021, April 1). *Association of Race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US*. JAMA network open. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8050743/#

Gaskin, D. J., Thorpe, R. J., McGinty, E. E., Bower, K., Rohde, C., Young, J. H., LaVeist, T. A., & Dubay, L. (2014, November). *Disparities in diabetes: The nexus of race, poverty, and place*. American journal of public health. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4021012/#

Greco, E. V., Russo, G., Giandalia, A., Viazzi, F., Pontremoli, R., & De Cosmo, S. (2019, May 31). *GLP-1 receptor agonists and kidney protection*. Medicina (Kaunas, Lithuania). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6630923/#

Gudeman, J., Jozwiakowski, M., Chollet, J., & Randell, M. (2013, March). *Potential Risks of Pharmacy Compounding*. Drugs in R&D. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627035/#

Knudsen, L. B., & Lau, J. (2019, April 12). *The discovery and development of liraglutide and semaglutide*. Frontiers in endocrinology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6474072/#

Kopp, K. O., Glotfelty, E. J., Li, Y., & Greig, N. H. (2022, December). *Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment*. Pharmacological research. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9712272/

Levi, J., Hill, A., Venter, F., & Wang, J. (n.d.). *Estimated minimum prices and lowest available national prices for antiobesity medications: Improving affordability and access to treatment*. Obesity (Silver Spring, Md.). https://pubmed.ncbi.nlm.nih.gov/36815242/

Ma, X., Liu, Z., Ilyas, I., Little, P. J., Kamato, D., Sahebka, A., Chen, Z., Luo, S., Zheng, X., Weng, J., & Xu, S. (2021, May 11). *GLP-1 receptor agonists (GLP-1RAS): Cardiovascular actions and therapeutic potential*. International journal of biological sciences. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8193264/#

Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021, April). *GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art*. Molecular metabolism. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8085572/#

NH;, K. K. E. Y. (n.d.). *Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment*. Pharmacological research. https://pubmed.ncbi.nlm.nih.gov/36372278/ Rosenstock, S., Whitman, S., West, J. F., & Balkin, M. (2014, October). *Racial disparities in diabetes*

mortality in the 50 most populous US cities. Journal of urban health : bulletin of the New York Academy of Medicine. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4199450/#

Rubino, D. M., Greenway, F. L., Khalid, U., O'Neil, P. M., Rosenstock, J., Sørrig, R., Wadden, T. A., Wizert, A., Garvey, W. T., & STEP 8 Investigators. (2022, January 11). *Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The step 8 randomized clinical trial*. JAMA. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8753508/#

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., & STEP 4 Investigators. (2021, April 13). *Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The step 4 randomized clinical trial*. JAMA. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7988425/#

Susan Z. Yanovski, M. (2021, July 13). *Progress in pharmacotherapy for Obesity*. JAMA. https://jamanetwork.com/journals/jama/article-abstract/2781519

Tung, E. L., Cagney, K. A., Peek, M. E., & Chin, M. H. (2017, December). *Spatial context and health inequity: Reconfiguring race, place, and poverty*. Journal of urban health : bulletin of the New York Academy of Medicine. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5722735/#

Wadden, T. A., Bailey, T. S., Billings, L. K., Davies, M., Frias, J. P., Koroleva, A., Lingvay, I., O'Neil, P. M., Rubino, D. M., Skovgaard, D., Wallenstein, S. O. R., Garvey, W. T., & STEP 3 Investigators. (2021, April 13). *Effect of subcutaneous semaglutide vs Placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The step 3 randomized clinical trial*. JAMA. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7905697/#