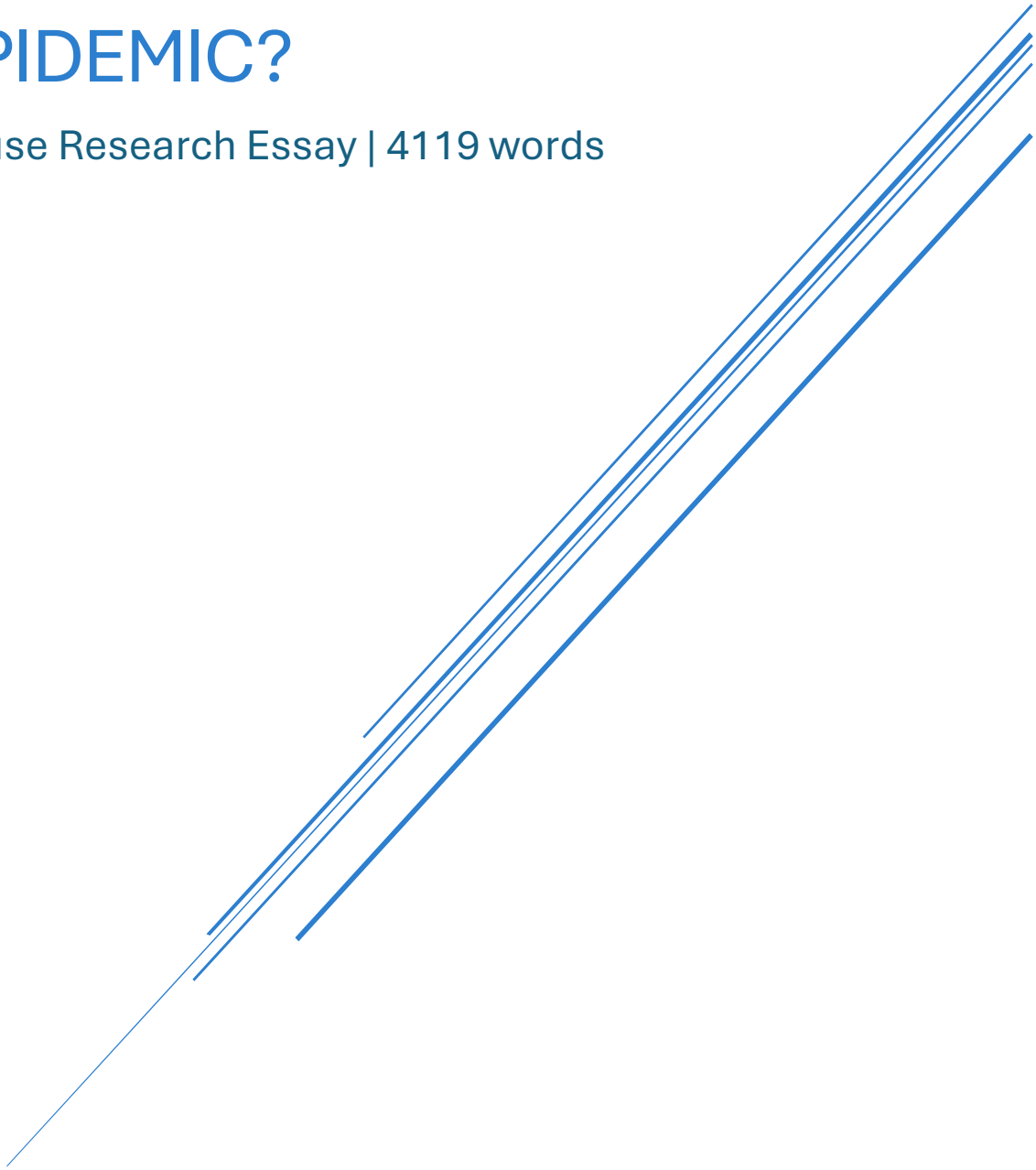
HOW DO GLP-1 RECEPTOR AGONIST WEIGHT LOSS DRUGS WORK AND WILL THEY BE THE SOLUTION TO THE OBESITY EPIDEMIC?

Rouse Research Essay | 4119 words



Abstract

Obesity is a major and increasing threat to global health and up until now treatments have been largely ineffective. Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are a new class of drugs initially investigated for treating diabetes which are now being developed as weight loss therapies.

This essay reviews current published literature on the efficacy, safety, and applicability of GLP-1RAs in the treatment of obesity.

This new class of drugs have proven to be remarkably successful weight loss agents in numerous clinical trials, especially in comparison with previous drug-based treatments. They are almost as effective as surgical interventions such as gastric banding, which is currently the best treatment option for severe obesity. Furthermore, not only do they cause significant weight loss, but they also reverse the negative consequences associated with obesity, including diabetes and heart disease. There are side effects with this class of drug, typically nausea and vomiting, but these tend to be mild. Unfortunately, upon discontinuation of GLP-1RAs, a considerable proportion of people regain their lost weight.

GLP-1RAs have proven to be a revolutionary medical treatment for obesity and new, more effective medications of this class are being designed, investigated, and brought to market at an unprecedented rate. Unfortunately, due to the issue of regaining weight, this treatment may have to be lifelong. Given the scale of the obesity epidemic, the demand for GLP-1RAs clearly outstrips the supply, particularly if these treatments are to be a long-term intervention. This has the potential to exacerbate global inequality in healthcare, as the high cost of the medication means it is unlikely to be accessible to everyone who could benefit.

Contents

Introduction 3

Mechanism for appetite regulation 3

The gut-brain axis 4

The role of hormones 4

The vagus nerve 5

Overriding the appetite regulation system 5

GLP-1 receptor agonists 5

Efficacy of GLP-1RA based drugs for weight loss 7

Health benefits of GLP-1RA based drugs 9

Physiological side effects 9

The issue of regaining weight 11

Wider issues 11

Conclusion 12

Acknowledgements 13

References 13

Introduction

By 2035, it is predicted that more than half of all adults will be overweight or obese which is estimated to cost the global economy over four trillion US dollars (World Obesity Atlas, 2023).

The World Health Organisation describes obesity as an "abnormal or excessive fat accumulation that presents a risk to health" and defines it as having a body mass index (BMI) of over thirty. BMI is the most widely accepted measure of a healthy weight, considering both height and mass.

Not only is obesity prevalent, but it can also lead to a multitude of health consequences including, but not limited to, those detailed below (see Figure 1). As a result, four million deaths were attributed to obesity worldwide in 2015 (GBD 2015 Obesity Collaborators, 2017).

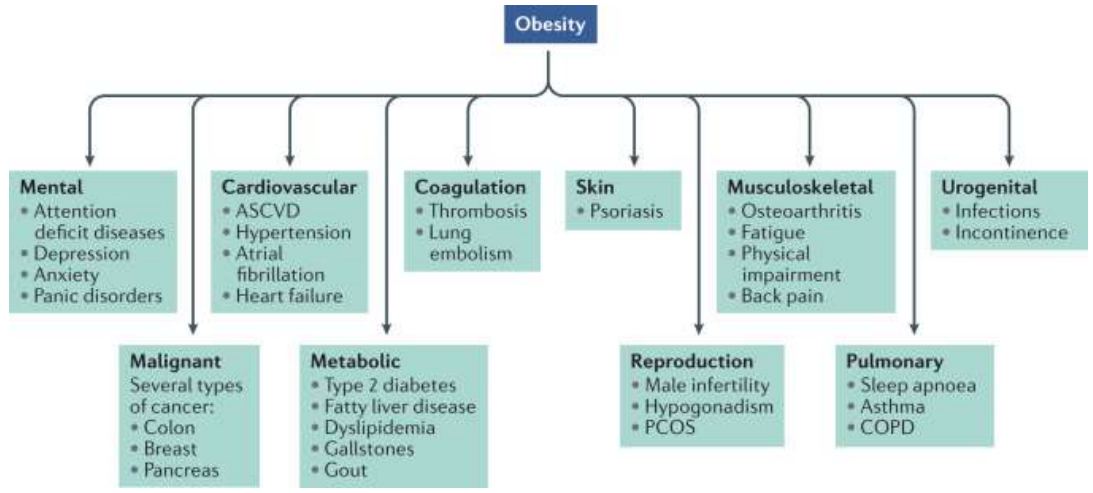


Figure 1. The health consequences of obesity (Müller, Blüher, Tschöp, & DiMarchi, 2022). *Abbreviations: ASCVD – atherosclerotic cardiovascular disease, PCOS – polycystic ovary syndrome, COPD – chronic obstructive pulmonary disease.*

There are numerous factors contributing to the obesity crisis such as increased access to energy dense food and reduced physical activity (Farooqi, 2024).

An effective treatment for obesity would have a significant impact on a global scale, especially as the prevalence is increasing sharply. Historically, there have been very few successful obesity treatments as the drivers for this condition are poorly understood. Therefore, the discovery of glucagon-like peptide 1 receptor agonists (GLP-1RAs) and the mechanism by which they work has the potential to revolutionise our approach to the obesity epidemic.

Mechanism for appetite regulation

To explore the possible treatments for obesity, an understanding of the regulation of body weight is required.

Historically, the regulation of body weight has been seen as a simple balance between our energy intake in the form of food and our energy expenditure in the form of physical activity, especially in the context of obesity. However, the homeostatic mechanism to control appetite

and weight regulation involves complex interactions between the gut, pancreas, and brain. This communication is known as the “gut-brain axis” (Pucci & Batterham, 2020).

The gut-brain axis

The brain receives information from environmental stimuli; energy storage organs like adipose (fat), bone and muscle tissue; nutrient levels in the blood and the type and quantity of food being absorbed.

The brain can then create the sensation of hunger or satiety and signal to parts of the body responsible for maintaining energy balance. Both the endocrine (secretion of hormones) and autonomic (unconscious part of the nervous system) are involved in communicating these signals to responsive tissues like liver and muscle (Woods & D'Alessio, 2008).

The gastrointestinal tract (GI tract) uses both neuronal and hormonal pathways to convey information about the quantity and type of nutrients absorbed. The most basic signals are sent through the vagus nerve in response to gut distension – when mechanoreceptors in the stomach and GI tract sense the walls expanding (Pucci & Batterham, 2020) (Druce & Bloom, 2006). However, there are also a plethora of hormones, released primarily from the gut and pancreas, which act on the brain and elsewhere.

The role of hormones

The hormones involved in appetite control can be split into two categories: regulating either adiposity or satiety (Woods & D'Alessio, 2008). The former are hormones released in proportion to the mass of adipose tissue, signalling directly to an area of the brain, called the hypothalamus, how much energy is stored as fat (Suzuki, Jayasena, & Bloom, 2012) and are therefore generally regarded to be regulators of long term energy balance (Pucci & Batterham, 2020). Insulin and amylin, secreted by the pancreas, and leptin, secreted by adipose tissue, fall into this group and all have anorexigenic effects, that is, they make a person feel hungry. They achieve this by affecting the sensitivity of key neurons to satiety hormones. For example, lower levels of insulin in the brain decreases the effect of satiety hormones and, consequently, the person feels hungry (Woods & D'Alessio, 2008). However, insulin’s primary role is to lower blood glucose levels (Druce & Bloom, 2006).

On the other hand, satiety hormones regulate hunger on a short term basis, either in anticipation of or due to the detection of food in the body (Pucci & Batterham, 2020). Many of these are gut hormones which can act in a paracrine manner, meaning they have effects locally in the GI tract, but are also significant in communication with appetite regulation areas of the central nervous system (Suzuki, Jayasena, & Bloom, 2012). Peptide YY (PYY) and glucagon like peptide 1 (GLP-1) both act to decrease food intake and are the major contributors to the “ileal brake” which is the negative feedback mechanism that decreases gut motility in response to nutrient intake (Spiller, et al., 1984). It also slows down gastric emptying and reduces bile acid and pancreatic secretions. They are both released from intestinal L cells and act on receptors in the vagus nerve (Suzuki, Jayasena, & Bloom, 2012). Other hormones released from the GI tract and the pancreas like pancreatic polypeptide (PP), oxyntomodulin (OXM), gastric inhibitory polypeptide (GIP) and cholecystokinin (CCK) act to decrease appetite in a similar way, by reducing gastric emptying. On the other hand, ghrelin is a hormone released from the stomach that acts to increase food intake by reducing insulin secretion and increasing gastric emptying. Glucagon is a further hormone to consider. It is released from the pancreas, its primary purpose being to increase blood glucose, but it also decreases food intake (Pucci & Batterham, 2020).

GLP-1 and GIP are also responsible for what is known as the “incretin effect” which is when oral (eaten) glucose causes a higher insulin response than the same amount of glucose injected into the bloodstream (Nauck & Meier, 2018). This is because GLP-1 and GIP act on pancreatic islet beta cells to enhance glucose-dependent insulin secretion in response to ingested nutrients, typically carbohydrates (Baggio & Drucker, 2007). Therefore, these incretin hormones stimulate insulin secretion, but only if blood sugar levels are elevated. It is for this reason that these hormones were used as anti-diabetic agents before their potential as weight loss drugs were realised.

The vagus nerve

The vagus nerve plays a significant role in appetite regulation. It has receptors for GLP-1, CCK and PYY. After detecting these hormones, it can pass information to the hypothalamus, which is the main appetite regulation centre in the brain. Both adiposity and satiety hormones can also act directly on the hypothalamus due to the incomplete blood-brain barrier in this area of the brain (Suzuki, Jayasena, & Bloom, 2012). Upper brain regions can then interpret these signals from the hypothalamus as well as higher cognitive functions like reward, habit and sensory inputs to increase or decrease appetite (Woods & D'Alessio, 2008).

Overriding the appetite regulation system

Internal and external influences can override the homeostatic mechanism for appetite regulation. The reward system in the brain is multi-faceted and can affect appetite based on environmental cues like food availability or palatability, habit, emotions, social interaction and hedonistic factors (Suzuki, Jayasena, & Bloom, 2012) (Woods & D'Alessio, 2008). Additionally, the genetic determinants of obesity have been well investigated (Bouchard, 2021). One of the major issues with obesity treatment is that risk factors are found on nearly every chromosome (Fall & Ingelsson, 2014). Therefore, while obesity has an estimated heritability of 40-70% (Maes, Neale, & Eaves, 1997) it is difficult to identify individual genes which could be targeted to cure obesity. There are a few notable monogenic conditions, an example being leptin deficiency, which has been successfully treated by administering leptin to patients (Montague, et al., 1997). This treatment, however, had negligible impact on patients without the deficiency (Heymsfield, et al., 1999).

Furthermore, there is an evolutionary drive to achieve a high body weight because, throughout much of human development, food has been scarce so it was advantageous to eat large amounts of food and store energy while it was available and safe to eat (Pucci & Batterham, 2020).

GLP-1 receptor agonists

Many of the hormones discussed above have been the focus of obesity treatment research, however most weight loss drugs currently in development are GLP-1RAs. GLP-1 itself cannot be used as a drug as it is rapidly cleared from the bloodstream, with a half-life of 1 to 2 minutes (Holst, 2007). GLP-1RAs are chemically modified versions of GLP-1 that resist enzymatic degradation. Other modifications vary between the specific GLP-1RAs but include the ability to bind to albumin, a major transporter protein in the blood, and resistance to breakdown by stomach acid for oral versions (Biopharma PEG, 2022).

They activate the native GLP-1 receptors which are found in numerous tissues like pancreatic islets, heart, kidney, intestine, vagus nerve, hypothalamus and brainstem (Baggio & Drucker,

2007) and bring about a variety of responses in the body outlined in the diagram below (see Figure 2).

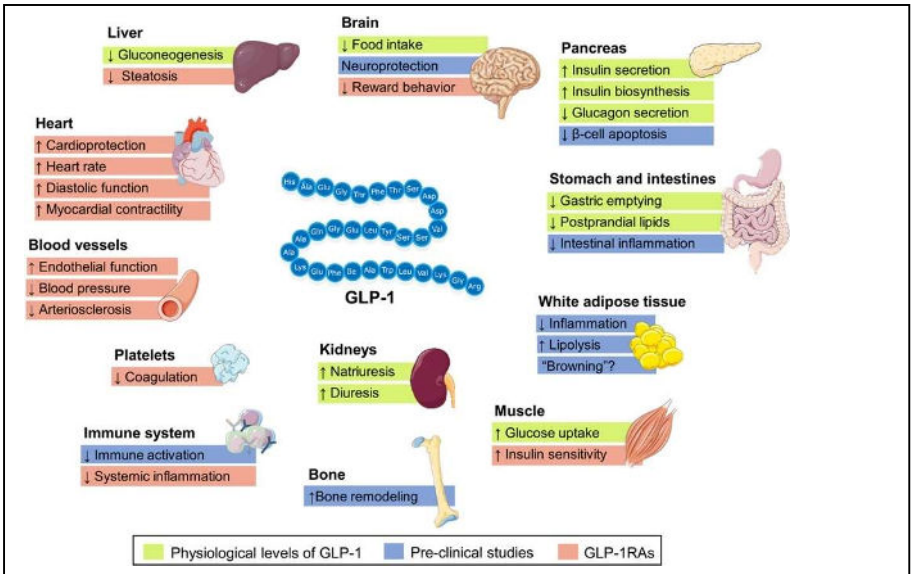


Figure 2. Physiological and pharmacological effects of GLP-1 and GLP-1RAs on the body (Andreasen, Andersen, Knop, & Vilsbøll, 2021)

There are a variety of GLP-1RA-based drugs previously or currently being tested or sold (see Table 1 below). GLP-1RAs were initially developed as medications for type 2 diabetes, and are still being used as such, but once their weight-loss applications were realised there has been significant development into their use in treating obesity.

Name	Brand names	Company	FDA approval (US)	Receptor agonist for which hormones	Administration
Exenatide	Byetta	Amylin & Eli Lilly	2005	GLP-1 (extracted from Gila lizard)	Twice-daily injection
	Bydueron		2012		Once-weekly injection
Liraglutide	Victoza	Novo Nordisk	2010	GLP-1	Once-daily injection
Dulaglutide	Trulicity	Eli Lilly	2014	GLP-1	Once-weekly injection
Semaglutide	Ozempic	Novo Nordisk	2017	GLP-1	Once-weekly injection
	Rybelsus		2019		Once-weekly injection
	Wegovy		2021		Once-daily oral
Tirzepatide	Mounjaro	Eli Lilly	2022	GLP-1, GIP	Once-weekly injection
	Zepbound		2023		Once-weekly injection
Retatrutide	"Triple G"	Eli Lilly	Still in testing	GLP-1, GIP, Glucagon	Once-weekly injection

Table 1. A summary of GLP-1RA based drugs, adapted from (Biopharma PEG, 2022) *and* (Andreasen, Andersen, Knop, & Vilsbøll, 2021).

The most commercially successful agents are semaglutide (Ozempic/Wegovy) and tirzepatide (Mounjaro/Zepbound). Eli Lilly is also currently investigating retatrutide, which is not currently on the market.

Investigations into combinations of GLP-1 and other receptor agonists, like tirzepatide and retatrutide, are progressing rapidly and are summarised in the diagram below (see Figure 3). The focus of this essay will remain on semaglutide, tirzepatide and retatrutide as they are either in the market or close to being so.

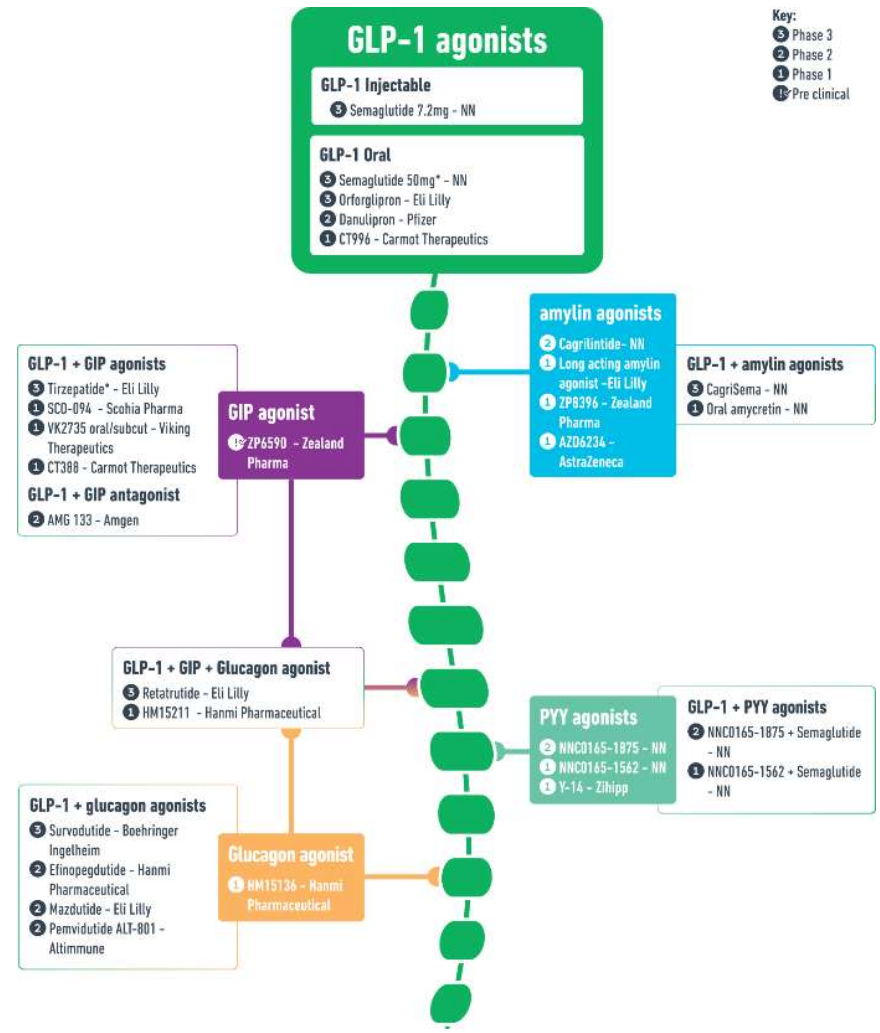


Figure 3. A summary of GLP-1RAs being used as the "backbone" for various anti-obesity medications (Melson, Ashraf, Papamargaritis, & Davies, 2024)

Efficacy of GLP-1RA based drugs for weight loss

According to the World Health Organisation International Clinical Trials Registry Platform, there have been over 100 clinical trials with results using semaglutide with the first taking place in 2008, resulting in 126 published clinical trial papers based on a PubMed search (12/03/24).

For the more newly developed agents, tirzepatide and retatrutide, the data is more limited with only 14 trials with results registered for tirzepatide and only one trial for retatrutide.

Despite the numerous semaglutide trials using different doses, different routes of administration and having different trial periods, which makes them difficult to compare directly, one thing they have in common is their success in achieving significant weight loss. There are over 40 published meta-analyses, many of which are overlapping. All of them report average weight losses of greater than 5%, with many exceeding 10%. For example, a large meta-analysis of 13 randomised controlled trials (with a total of roughly 5,800 overweight or obese adults receiving once-weekly injected semaglutide or a placebo for 12-108 weeks) showed that treatment with semaglutide gave a -10.0% mean difference in weight compared to the placebo and a 9kg mean absolute weight loss in comparison (Zhang, et al., 2023).

Trials for oral, rather than subcutaneous semaglutide, show similar success. In the OASIS 1 trial, participants who received 50mg of oral semaglutide for 68 weeks had bodyweight reductions of 12.7% compared to the placebo (Knop, et al., 2023). This is important because oral administration is often favourable for users over a subcutaneous (into the fatty layer under the skin) injection.

Treatment with tirzepatide (GLP-1 and GIP receptor agonists) has shown even more significant weight loss outcomes in clinical trials. A meta-analysis comparing subcutaneous semaglutide with tirzepatide for the treatment of obesity and overweight showed that the placebo-subtracted percentage different in body weight was -12.9% for semaglutide and -19.2% for tirzepatide (Müllertz, Sandsdal, Jensen, & Torekov, 2024).

Retatrutide (GLP-1, GIP, glucagon receptor agonists) is still in the earlier stages of development, but the trial by Eli Lilly shows great promise for its use in treating obesity. At 48 weeks, the average percentage change in body weight was -22.1% for once-weekly subcutaneous retatrutide compared to the placebo for the highest dose tested (12mg). Lower doses also achieved considerable weight losses, the lowest (1mg) still being significant at -8.7% (Jastreboff, et al., 2023).

When compared to previous weight loss treatments, semaglutide has performed better in trials. A meta-analysis comparing semaglutide to other non-surgical interventions (looking at data from 168 trials with nearly 98,000 patients total) shows that, whilst all drugs were associated with a greater weight loss than the placebo, semaglutide had the greatest mean difference in body weight of -10.42% (Iannone, et al., 2023). The other drugs tested included alternative GLP-1RAs like liraglutide plus orlistat which reduces the absorption of fat into the intestines, phentermine which reduces hunger by stimulating the flight or fight response (Rogers, 2024), and naltrexone or lorcaserin which activate neuroreceptors involved in the hunger pathway (Ornellas & Chavez, 2011). Semaglutide also performed significantly better than “standard care” lifestyle interventions (usually intensive behavioural therapy and calorie restriction).

Bariatric surgeries such as sleeve gastrectomy (which reduces effective stomach volume) and gastric bypass are currently considered the most effective weight loss treatment and are more effective than semaglutide (Klair, et al., 2023). Five years after treatment, patients who underwent bariatric surgery maintained an average weight loss of 25% of their initial body weight compared to weight losses of 9.6% for 68 weeks of semaglutide, and in many semaglutide patients some of this weight was regained after treatment was ended. However, hormone-based therapies are associated with fewer complications and are considerably less invasive. The adverse effects normally associated with bariatric surgery include nutrient deficiencies, gallstones, dumping syndrome (an early release of stomach contents, characterised by nausea and diarrhoea) and gastric ulcers. Additionally, bariatric surgery is

believed to achieve such effective weight loss through a modulation of gut hormones, including GLP-1, rather than by restricting stomach size alone (Pucci & Batterham, 2020). Therefore GLP-1RAs could be considered to mimic the actions of bariatric surgery. As GLP-1RA drug research is advancing rapidly, newer therapeutics are likely to reach the same weight loss outcomes as surgery in the near future.

Health benefits of GLP-1RA based drugs

There is no doubt that GLP-1RAs are effective in causing significant weight loss. However, a more important question is whether this weight loss has an overall positive impact on a person's health.

Whilst the focus of this essay is to consider the treatment of obesity, it is important to note the efficacy of GLP-1RAs as diabetes medications, as they were originally developed for this purpose. A meta-analysis of 33 studies of durations ranging from 5 weeks to 8 years, showed that semaglutide was associated with a significant reduction in HbA1c levels (which is the best recognised marker for diabetes and diabetes-related complications); additionally it reduced the risk of major cardiovascular events such as heart failure and stroke (Wang, Wang, Wang, & Luan, 2024).

Aside from their applications in diabetes, GLP1-RAs have been shown to be an effective treatment for cardiovascular disease. Weight losses of just 10%, which are often achieved using semaglutide and similar treatments, have been proven to improve glycaemic control, reduce blood pressure and reduce cholesterol levels. All these outcomes improve overall metabolic and cardiovascular health, reducing the risk of heart disease, heart attacks and strokes (Goldstein, 1992). Additionally, a trial specifically performed to investigate the impact of semaglutide on non-diabetic patients with cardiovascular disease showed a reduction in serious cardiovascular outcomes such as death, heart attacks or strokes. 701 of the 8801 participants in the placebo group experienced a severe cardiovascular event compared to 569 of the 8803 in the semaglutide group, which is a 20% reduction in adverse cardiovascular outcomes (Lincoff, et al., 2023). A further analysis of these data presented at the European Congress of Obesity this year suggested that the cardioprotective properties of semaglutide may be independent of the percentage weight loss, with participants losing less than 5% of their weight experiencing the same benefits as those losing more than 5% (Deanfield, 2024).

The weight loss due to semaglutide is often accompanied by other positive health impacts. These include decreasing levels of inflammatory proteins and reducing waist circumference (Wilding, et al., 2022). A decrease in waist circumference is significant because this indicates that the weight lost is due to a reduction in visceral fat (fat stored around the organs), which is considered the most damaging to health (Snijder, van Dam, Visser, & Seidell, 2006).

Treatment with semaglutide has a positive impact on eating habits as well as overall energy intake. When compared to the placebo, patients taking semaglutide experienced fewer food cravings, a better overall control of eating and a reduced preference for high fat foods (Blundell, et al., 2017). Therefore, rather than solely reducing appetite, treatment with semaglutide helps to alter food choices which may contribute to its efficacy as a weight loss treatment.

Physiological side effects

Whilst the efficacy of GLP-1RAs for weight loss is indisputable, these drugs are not free from side effects or potential long term health risks.

The side effects of subcutaneous semaglutide discussed below have been well documented and summarised in a large meta-analysis (Smits & Raalte, 2021).

The most significant side effects reported were gastrointestinal: including nausea, diarrhoea, and vomiting (see Table 2 below).

	% that experience side effects	
Side effect	**Placebo**	**Semaglutide**
Nausea	3.3 - 8.0	11.4 - 20
Diarrhoea	1.5 - 6.0	5.0 - 11.0
Vomiting	2.0 - 3.0	4.5 – 11.3

Table 2. The incidence of GI side effects when taking semaglutide compared to placebo. Adapted from (Smits & Raalte, 2021).

The GI side effects from semaglutide can be significant enough for participants to discontinue treatment during trial periods. The reason for these side effects is not well understood but decreased gut motility is a likely mechanism. Unfortunately, as decreased gut motility may also be responsible for weight loss, this side effect may be difficult to avoid. For this reason, semaglutide tends be administered as an escalating dose in an attempt to reduce GI side effects. When tirzepatide was compared to semaglutide, there was more weight loss but a similar incidence of side effects, suggesting it will be a better weight loss treatment (Tan, et al., 2023).

Despite concern, clinical trials have not shown an increased risk of pancreatitis, pancreatic cancer, or acute kidney injury (due to fluid loss). Also, the possible association between GLP-1RAs and thyroid cancer, due to potential increased proliferation of thyroid tissue, is difficult to establish given the low prevalence of this condition. However, an increased incidence of gallbladder inflammation is associated with GLP-1RA treatment, but these events were not severe.

Given that GLP-1RAs are used to treat high blood sugar in diabetic patients, a significant concern for these therapies is the risk of hypoglycaemia (low blood sugar). However, unlike insulin injections, GLP-1RAs cause a glucose-dependent release of insulin and the risk of hypoglycaemia is low. This is best evidenced by a number of overdose cases. In three separate case reports significant (up to 20-fold) overdosing incidents with semaglutide did not lead to hypoglycaemic events (Wiener, Gnirke, Vassallo, Smith, & Su, 2024). Similarly, an overdose of liraglutide over the course of 7 months did not cause any signs of hypoglycaemia (Bode, Egg, Wallesch, & Hermanns-Clausen, 2013). However, in all four cases the patients experienced GI side effects of nausea and vomiting.

Additionally, liraglutide and semaglutide were investigated by the European Medicines Agency after 3 incidents of suicidal thoughts were reported in Iceland. However, a study of around 240,000 patients with obesity and 1.6 million patients with type 2 diabetes showed that taking semaglutide decreased the risk of suicidal thoughts by 49-73% when compared to other weight loss medications. Therefore, the suggestion that GLP-1RA treatment increases the risk of suicide is not supported (Wang, et al., 2024).

A possible concern for any non-native peptide hormone-based therapy is that the immune system will raise antibodies which act to neutralise the action of the drug in question. This has

not been demonstrated with semaglutide but has been shown in trials of earlier GLP-1RAs such as exenatide and dulaglutide (Filippatos, Panagiotopoulou, & Elisaf, 2014).

The issue of regaining weight

Despite the success of GLP-1RA treatment in causing weight loss, the most significant drawback of this type of drug is that many patients rapidly regain their lost weight after stopping treatment.

An extension of the STEP-1 trial continued to monitor participants after 68 weeks of treatment. Following a mean weight loss of 17.3% in the treatment period, participants regained an average of 11.6%, which is starkly demonstrated on the graph below (see Figure 4). Consequently, long-term weight losses were only about 5% by week 120. Unfortunately, the cardiometabolic improvements (e.g. in blood pressure, cholesterol levels and HbA1c) during the semaglutide treatment were also often lost (Wilding, et al., 2022).

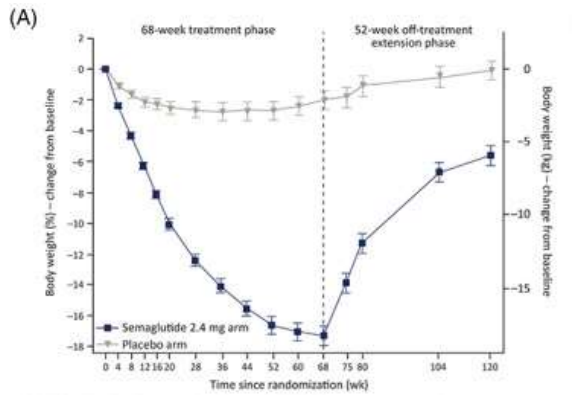


Figure 4. The change in body weight after stopping semaglutide treatment (Wilding, et al., 2022)

However, some trials have yielded more optimistic data. A large-scale investigation of around 20,000 patients showed that 56.2% of patients either maintained their weight loss or lost additional weight (Bartelt, Mast, Deckert, Gracianette, & Joyce, 2024). Whilst this shows that GLP-1RAs are a successful treatment for many, it also suggests that lifelong treatment may be required for a considerable number of people. This reduces the utility of this class of drug.

Wider issues

There are also wider socioeconomic issues associated with GLP-1RA based drugs.

Firstly, given their success in causing significant weight loss, there is now a high demand for drugs like Wegovy from a wide range of people, not just those who are overweight, obese, or diabetic. This demand has been fuelled by a "media hype" as numerous celebrities are open about using GLP-1RAs.

Potentially the most dangerous issue associated with the short supply is the illegal market for fake GLP-1RA drugs, often through social media platforms. There have been reports of people falling ill after using unlicensed versions of medications claiming to be semaglutide. This online black market has been difficult to control despite numerous arrests of those illegally providing

the drug and attempts by Novo Nordisk to shut down illegal websites and keep stricter quality controls (Walsh & Rai, 2023).

Furthermore, suppliers of GLP-1RAs (like Novo Nordisk and Eli Lilly) are struggling to keep up with the enormous demands. As a result, the UK experienced delays in receiving a supply of Wegovy in 2023 (Wilson, 2023). Even when supplied, the UK still has a limited stock of these medications, so GLP-1RAs are only legally accessible from specialist NHS weight loss management services and some private clinics. Additionally, GLP-1RA treatments are expensive in the United States, costing $1349/month compared to $300/month in two European countries (Wilson, 2023) and the providers are turning over huge profits. By the end of 2023, Novo Nordisk's annual net profit had risen by 51%, meaning that Denmark now publishes the drugs industry separate to other economic statistics (Murray, 2024). Therefore, although many people could benefit from this obesity and diabetes medication, supply issues and high costs have reduced accessibility and will increase global health inequality.

Conclusion

If the question is whether these drugs cause weight loss, the conclusion is absolutely. Large scale trials have proven over and over that these drugs make people lose weight by mimicking a hormone naturally produced in the body to signal short-term satiety and reduce appetite.

However, this is not equivalent to them being a solution to the obesity crisis.

Firstly, there is the major issue of weight regain. This has significant consequences for the future of these drugs. They are only approved for use in the UK for 2 years, but GLP-1RAs may have to be a lifelong treatment for many people, rather than the hoped for one-off "reset button". The complex interactions between environmental, physiological, psychological, and genetic factors responsible for the initial weight gain are still likely to be present when the drug is stopped. This raises the question of whether GLP-1RA treatment addresses the root cause of the obesity epidemic. However, irrespective of the cause of obesity, for the first time we have an effective non-surgical intervention to address the negative health consequences of excess weight gain.

The possible lifelong nature of treatment with these drugs has further consequences because, for some people, the GI side effects may eventually start to outweigh the weight loss benefits and they may just get sick of being sick.

Given the huge scale of the obesity epidemic, the global supply of GLP-1RAs does not meet the demand, let alone the demand for a lifelong treatment. The issue may be exacerbated by the high cost set by drugs companies like Novo Nordisk and Eli Lilly who are returning huge profits. This means many people who could benefit from these treatments will not have access to them.

However, GLP-1RAs are still a dramatically significant achievement in the field of medicine.

This field is still rapidly developing, even during the writing of this essay new combination therapies supplementing GLP-1RAs with other gut hormone analogues are being investigated (see Figure 3). By targeting multiple elements of the appetite regulation pathway, these therapies are likely to be even more effective, as has been demonstrated by the recent success of the retatrutide trial. Additionally, this raises the possibility of tailoring the mixture of hormone analogues in these treatments to individual patient circumstances such as diabetes or cardiovascular disease.

In conclusion, although GLP-1RAs will not solve the obesity epidemic in the near future, they are already having a significant positive impact on the lives of many people with obesity. Given the pace and success of current research, this will almost certainly improve as treatments are further refined.

Acknowledgements

I would like to thank my supervisor Mr Couper-Marsh for providing invaluable help and support through the entire research process.

References

Andreasen, C. R., Andersen, A., Knop, F. K., & Vilsbøll, T. (2021, July 17). How glucagon-like peptide 1 receptor agonists work. *Endocrine Connections, 10*(7), R200–R212. doi:https://doi.org/10.1530/EC-21-0130

Baggio, L. L., & Drucker, D. J. (2007, May). Biology of incretins: GLP-1 and GIP. *Gastroenterology, 132*(6), 2131-57. doi:10.1053/j.gastro.2007.03.054

Bartelt, K., Mast, C., Deckert, J., Gracianette, M., & Joyce, B. (2024, January 23). *Many Patients Maintain Weight Loss a Year After Stopping Semaglutide and Liraglutide*. Retrieved May 4, 2024, from Epic Research: https://www.epicresearch.org/articles/many-patients-maintain-weight-loss-a-year-after-stopping-semaglutide-and-liraglutide

Biopharma PEG. (2022, September 22). *Evolution of GLP-1 Receptor Agonists for Diabetes Treatment*. Retrieved from biochempeg: https://www.biochempeg.com/article/299.html

Blundell, J., Finlayson, G., Axelsen, M., Flint, A., Gibbons, C., Kvist, T., & Hjerpsted, J. B. (2017, September). 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. doi:10.1111/dom.12932

Bode, S. F., Egg, M., Wallesch, C., & Hermanns-Clausen, M. (2013, July). 10-fold liraglutide overdose over 7 months resulted only in minor side-effects. *Journal of Clinical Pharmacology, 53*(7), 785-6. doi:10.1002/jcph.94

Bouchard, C. (2021, April 26). Genetics of Obesity: What We Have Learned Over Decades of Research. *Obesity, 29*(5), 802-820. doi:https://doi.org/10.1002/oby.23116

Deanfield, J. (2024). Relevance of Body Weight and Weight Change on Cardiovascular Benefit with Semaglutide: A Pre-specified Analysis of the SELECT Trial. *ECO 2024 Abstracts*, (p. 1233). Venice.

Druce, M., & Bloom, S. R. (2006, February). The regulation of appetite. *Archives of disease in childhood, 91*(2), 183-187. doi:10.1136/adc.2005.073759

Fall, T., & Ingelsson, E. (2014, January 25). Genome-wide association studies of obesity and metabolic syndrome. *Molecular and Cellular Endocrinology, 382*(1), 740-757. Retrieved March 13, 2024

Farooqi, S. (2024, January 17). Dawn of a new era in the treatment of obesity.

Filippatos, T. D., Panagiotopoulou, T. V., & Elisaf, M. S. (2014). Adverse Effects of GLP-1 Receptor Agonists. *The Review of Diabetic Studies, 11*(3), 202-230. doi:10.1900/RDS.2014.11.202

GBD 2015 Obesity Collaborators. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *The New England Journal of Medicine, 337*(1), 13-27. doi:10.1056/NEJMoa1614362

Goldstein, D. J. (1992, June). Beneficial health effects of modest weight loss. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, 16*(6), 397-415.

Heymsfield, S. B., Greenberg, A. S., Fujioka, K., Dixon, R. M., Kushner, R., Hunt, T., . . . McCamish, M. (1999, October 27). Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA, 282*(16), 1568-1575. doi:10.1001/jama.282.16.1568

Holst, J. J. (2007). The Physiology of Glucagon-like Peptide 1. *Physiological Reviews, 87*(4), 1409-1439. Retrieved April 29, 2024

Iannone, A., Natale, P., Palmer, S. C., Nicolucci, A., Rendina, M., Giorgino, F., . . . Strippoli, G. F. (2023, May 31). Clinical outcomes associated with drugs for obesity and overweight: A systematic review and network meta-analysis of randomized controlled trials. *Diabetes, Obesity and Metabolism, 25*(9), 2535-2544. doi:doi.org/10.1111/dom.15138

Jastreboff, A. M., Kaplan, L. M., Frías, J. P., Wu, Q., Du, Y., Gurbuz, S., . . . Hartman, M. L. (2023, June 26). Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. *The New England Journal of Medicine, 389*(6), 514-526. doi:10.1056/NEJMoa2301972

Klair, N., Patel, U., Saxena, A., Patel, D., Ayesha, I. E., Monson, N. R., & Ramphall, S. (2023, September 29). What Is Best for Weight Loss? A Comparative Review of the Safety and Efficacy of Bariatric Surgery Versus Glucagon-Like Peptide-1 Analogue. *Cureus, 15*(9), e46197. doi:10.7759/cureus.46197

Knop, P. F., Aroda, V. R., do Vale, R. D., Holst-Hansen, T., Laursen, P. N., Rosenstock, J., . . . Garvey, W. T. (2023, August 26). Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet, 402*(10403), 705-719. Retrieved April 30, 2024

Lincoff, A. M., Brown-Frandsen, K., Colhoun, H. M., Deanfield, J., Emerson, S. S., Esbjerg, S., . . . Ryan, D. H. (2023, December 14). Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *New England Journal of Medicine, 389*(24), 2221-2232. doi:10.1056/NEJMoa2307563

Maes, H. H., Neale, M., & Eaves, L. J. (1997, July). Genetic and environmental factors in relative body weight and human adiposity. *Behavior genetics, 27*(4), 325-351. doi:10.1023/a:1025635913927

Melson, E., Ashraf, U., Papamargaritis, D., & Davies, M. J. (2024, February 1). What is the pipeline for future medications for obesity? *International Journal for Obesity*, 1476-5497. doi:10.1038/s41366-024-01473-y

Montague, C. T., Farooqi, I. S., Whitehead, J. P., Soos, M. A., Rau, H., Wareham, N. J., . . . O'Rahilly, S. (1997, June 26). Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature, 387*(6636), 903-908. doi:10.1038/43185

Müller, T. D., Blüher, M., Tschöp, M. H., & DiMarchi, R. D. (2022, March). Anti-obesity drug discovery: advances and challenges. *Nature Reviews Drug Discovery, 21*(3), 201-223. doi:10.1038/s41573-021-00337-8

Müllertz, A. L., Sandsdal, R. M., Jensen, S. B., & Torekov, S. S. (2024, March 11). Potent incretin-based therapy for obesity: A systematic review and meta-analysis of the efficacy of semaglutide and tirzepatide on body weight and waist circumference, and safety. *Obesity Reviews, 25*(5), e13717. doi:10.1111/obr.13717

Murray, A. (2024, February 11). Wegovy, the 'Viagra' of weight-loss drugs flying off the shelves. *BBC News*. Retrieved May 11, 2024, from https://www.bbc.co.uk/news/business-68226369

Nauck, M. A., & Meier, J. J. (2018, January 24). Incretin hormones: Their role in health and disease. *Diabetes, obesity and metabolism, 20*(S1), 5-21. Retrieved March 17, 2024

Ornellas, T., & Chavez, B. (2011, May). Naltrexone SR/Bupropion SR (Contrave): A New Approach to Weight Loss in Obese Adults. *P & T : a peer-reviewed journal for formulary management, 36*(5), 255-262.

Pucci, A., & Batterham, R. L. (2020, April 25). *Endocrinology of the Gut and the Regulation of Body Weight and Metabolism*. Retrieved March 12, 2024, from Endotext: https://www.ncbi.nlm.nih.gov/books/NBK556470/

Rogers, K. (2024, March 7). *phentermine*. Retrieved April 30, 2024, from Encyclopedia Britannica: https://www.britannica.com/science/phentermine

Smith, I., Hardy, E., Mitchell, S., & Batson, S. (2022, October 13). Semaglutide 2.4 Mg for the Management of Overweight and Obesity: Systematic Literature Review and Meta-Analysis. *Diabetes, Metabolic Syndrome and Obesity, 15*, 3961-3987. Retrieved April 30, 2024

Smits, M. M., & Raalte, D. H. (2021, July 7). Safety of Semaglutide. *Frontiers in Endocrinology, 12*, 645563. doi:10.3389/fendo.2021.645563

Snijder, M., van Dam, R., Visser, M., & Seidell, J. (2006, February). What aspects of body fat are particularly hazardous and how do we measure them? *International Journal of Epidemiology, 35*(1), 83-92. Retrieved May 11, 2024

Spiller, R. C., Trotman, I. F., Higgins, B. E., Ghatei, M. A., Grimble, G. K., Lee, Y. C., . . . Silk, D. B. (1984). The ileal brake--inhibition of jejunal motility after ileal fat perfusion in man. *Gut, 25*(4), 365-74. doi:10.1136/gut.25.4.365

Suzuki, K., Jayasena, C. N., & Bloom, S. R. (2012, August 1). Obesity and Appetite Control. *Experimental Diabetes Research*. doi:10.1155/2012/824305

Tan, B., Pan, X.-H., Chew, H. S., Goh, R. S., Lin, C., Anand, V. V., . . . Khoo, C. M. (2023, May 31). Efficacy and safety of tirzepatide for treatment of overweight or obesity. A systematic review and meta-analysis. *International Journal of Obesity, 47*, 677-685. doi:doi.org/10.1038/s41366-023-01321-5

Tan, H. C., Dampil, O. A., & Marquez, M. M. (2022). Efficacy and Safety of Semaglutide for Weight Loss in Obesity Without Diabetes: A Systematic Review and Meta-Analysis. *Journal of the ASEAN Federation of Endocrine, 37*(2), 65-72. doi:10.15605/jafes.037.02.14

Walsh, A., & Rai, P. (2023, November 15). Weight loss injection hype fuels online black market. *BBC News*. Retrieved May 5, 2024, from BBC News: https://www.bbc.co.uk/news/health-67414203#:~:text=A%20woman%20who%20was%20illegally,ingredient%20in%20Ozempic%20%2D%20from%20Instagram.

Wang, S., Wang, S., Wang, Y., & Luan, J. (2024, February). Glycemic Control, Weight Management, Cardiovascular Safety, and Cost-Effectiveness of Semaglutide for Patients with Type 2 Diabetes Mellitus: A Rapid Review and Meta-analysis of Real-World Studies. *Diabetes Therapy, 15*(2), 497-519. doi:10.1007/s13300-023-01520-3

Wang, W., Volkow, N. D., Berger, N. A., Davis, P. B., Kaelber, D. C., & Xu, R. (2024, January 5). Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nature Medicine, 30*, 168-176. doi:10.1038/s41591-023-02672-2

WHO. (2024). *Obesity*. Retrieved March 13, 2024, from World Health Organization: https://www.who.int/health-topics/obesity#tab=tab_1

Wiener, B. G., Gnirke, M., Vassallo, S., Smith, S. W., & Su, M. K. (2024, February). Challenges with glucagon-like peptide-1 (GLP-1) agonist initiation: a case series of semaglutide overdose administration errors. *Clinical Toxicology, 62*(2), 131-133. doi:10.1080/15563650.2024.2322049

Wilding, J. P., Batterham, R. L., Davies, M., Van Gaal, L. F., Kandler, K., Konakli, K., . . . Group, S. 1. (2022, August). Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes, Obesity and Metabolism, 24*(8), 1553-1564. doi:10.1111/dom.14725

Wilson, C. (2023, September 9). Why is the Wegovy weight-loss treatment so hard to get hold of? *New Scientist, 259*(3455), 17. Retrieved May 5, 2024

Woods, S. C., & D'Alessio, D. A. (2008, November 1). Central control of body weight and appetite. *The Journal of clinical endocrinology and metabolism, 93*, s37-s50. doi:10.1210/jc.2008-1630

World Obesity Atlas. (2023, March). Retrieved March 13, 2024, from World Obesity Federation: https://data.worldobesity.org/publications/?cat=19

Zhang, R., Hou, Q. C., Li, B. H., Deng, L., Yang, Y. M., Li, T. X., . . . Shuai, P. (2023, June 26). Efficacy and safety of subcutaneous semaglutide in adults with overweight or obese: a subgroup meta-analysis of randomized controlled trials. *Frontiers in Endocrinology, 14*. doi:10.3389/fendo.2023.1132004