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GLP-1 Receptor Agonists in the Pharmaceutical Landscape: An Analysis of Current Applications, Market Barriers, and Future Developments

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Abstract

In recent decades metabolic disorders have emerged as one of the most pressing public health challenges globally, with obesity playing a crucial role in driving this trend. Despite the availability of various treatment options ranging from lifestyle modification to surgical interventions, sustainable management of obesity and its complications remains challenging and in need of more effective solutions. This thesis explores the impact of GLP-1 RAs, initially developed for Type 2 diabetes treatment, as innovative pharmacotherapeutic tools for obesity management. The analysis focuses on their clinical efficacy, mechanisms of action, market dynamics, and regulatory barriers, with particular attention to their potential to revolutionize the treatment of metabolic disorders. Evidence from clinical trials demonstrates promising outcomes in terms of sustainable weight loss and metabolic improvements. This thesis also discusses the expansion of the GLP-1 RA market across indications, access challenges and reimbursement considerations for key European markets, outlining how these therapies are reshaping the pharmaceutical landscape beyond obesity and diabetes through pipeline analysis.

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Introduction

The past half-century has witnessed a profound shift in public health dynamics, with metabolic disorders taking center stage as one of the most pressing challenges of our times. Once the rich man's diseases, these conditions have reached epidemic proportions globally. The rapid rise of obesity, in particular, has transformed from an individual health concern to a significant societal and economic burden for many nations. In 2022, the WHO recorded 2.5 billion overweight adults, of which 890 million could be classified as obese. These numbers represented a staggering 43% of men and 44% of women (WHO, 2024).

Metabolic disorders encompass a range of conditions characterized by the body's inability to conduct normal metabolic processes. Among them, obesity stands out due to its high prevalence and being a driver of comorbidities such as, but not limited to, Type 2 Diabetes (T2D), cardiovascular diseases such as hypertension, dyslipidaemia and heart failure, osteoarthritis, ischemic stroke, breast cancer, prostate cancer, obstructive sleep apnea, depression and other mental health problems (Guh et al. 2009, Klop et al. 2013, Adair et al. 2020, Depres et al. 2006, Mitchell et al. 2015, Dong et al. 2004, Bray 2004).

The pathophysiology of obesity is complex, involving an interplay of genetic, environmental, and behavioral factors. Traditionally, obesity is thought to originate from a chronic imbalance between energy intake and caloric expenditure, leading to accumulation of adipose tissue in the body over time. Factors such as overeating, exacerbated by the availability of energy dense and low-nutrient foods combined with insufficient physical activity, are central to this imbalance. More recently, the focus has shifted to include heritable genetic factors such as the propensity to store excess energy as fat, hormonal responses that regulate hunger, metabolism and fat storage, as well as environmental and socioeconomic factors. Therefore, the current perspective considers obesity as a chronic disease with complex etiology, associated with high mortality rates (Kyle 2016).

The medical costs associated with the treatment of obesity are staggering and reach far beyond individual implications. A review analyzing the economic costs of adult obesity found that total costs of direct and indirect obesity in Germany accounted for 0.47-0.61% of GDP, with individual costs reaching up to €1873 per patient per year (von Lengerke and Krauth, 2011). The economic impact of the disease is varied, ranging from direct medical costs of obesity and its related diseases, to increased work absenteeism and lower work productivity, as well as health insurance and disability insurance costs and a marked decrease in quality of life (Anekwe et al. 2020). A 2014 McKinsey analysis estimated the global cost of obesity at 2.8% of global GDP (Dobbs, 2014). Obesity disproportionately affects minorities and the disadvantaged portions of the population, including people with disabilities, living in rural areas, and marginalized groups (Byrd et al. 2018, Newsome et al. 2021). It is not surprising to find disparities in access and quality of obesity care, exacerbated by the strong social stigma associated with the disease and its manifestations (Washington et al. 2023, Newsome et al. 2021). Foster et al. (2003) found that, in a sample of 5000 physicians, about 50% viewed obese patients as awkward, unattractive, ugly and noncompliant.

Despite the availability of various treatment options, including lifestyle intervention, pharmacological tools and bariatric surgery, managing obesity and its related complications remains a challenge. Traditional approaches often fail to produce sustainable weight loss, with many patient cycling between periods of weight loss and weight gain. This highlights a critical unmet need for more effective, long-lasting treatments that address the underlying mechanisms of obesity rather than its manifest symptomatology.

In this context, the emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represents a potential paradigm shift and a historical development in the treatment of obesity and related metabolic disorders. Initially developed for the treatment of Type 2 Diabetes, GLP-1 RAs have demonstrated significant efficacy in promoting weight loss by enhancing satiety, reducing appetite, and improving glucose metabolism. As research progresses, these agents are poised to play an increasingly central role in combating the obesity epidemic.

This thesis will explore the implications of GLP-1 receptor agonists in the treatment of metabolic disorders, with a particular focus on obesity. It will examine how these agents are revolutionizing patient care, reshaping the pharmaceutical landscape, and prompting new policy considerations, offering a comprehensive analysis of their potential to change the future

of metabolic disorder management. The chapters are structured as follows: Chapter 1 offers an overview of obesity and metabolic disorders, focusing on perception, classification, and relevance. Chapter 2 reviews current obesity treatments, including an introduction to GLP-1 receptor agonists. Chapter 3 examines market dynamics, competitive landscape, regulatory challenges, and access and reimbursement considerations, with particular attention dedicated to the current GLP-1 pipeline and its implications. The conclusion will provide a summary of findings and implications.

CONTENTS

1 An Overview of Obesity and Metabolic Disorders

Obesity has emerged as one of the most significant public health challenges of the 21st century. As its prevalence continues to rise globally, so do its associated comorbidities, including metabolic disorders such as Type 2 Diabetes (T2D), cardiovascular disease, liver disease, and hypertension. The complex nature of obesity, which involves genetic, environmental, and behavioral factors, underscores the importance of understanding and recognizing it as a chronic disease.

According to Bray (2004), obesity should be considered a chronic disease in the same sense as hypertension and atherosclerosis. More adipose tissue implies a dysfunctional production of fat cells, with metabolic implications such as the development of insulin resistance, diabetes, cardiovascular disease and hypertension caused by the proinflammatory state of obesity. Additionally, excess cytokine release is associated with an increase in cancer risk. Bray (2004) considers the excess storage of fat in hyperplastic and hypertrophic cells as the pathological lesion of obesity, whose consequences encompass other diseases including but not limited to diabetes mellitus, gallbladder disease, osteoarthritis, heart disease, and some forms of cancer. Therefore, the relationship between obesity and metabolic disorders is reciprocal, with obesity often serving as both a cause and a consequence of metabolic dysfunction.

This chapter will explore obesity's multifactorial nature, its classification, epidemiology, and the critical links between obesity and metabolic disorders.

1.1 Definition and Classification of Obesity

Obesity is typically defined as an excessive accumulation of body fat that presents a risk to health. As such, the most widely used metric for defining and assessing obesity is the Body Mass Index (BMI), a simple index of weight-for-height that is calculated as a person's weight in kilograms divided by the square of their height in meters (kg/m²). According to the World Health Organization (WHO, 2024), a BMI of 30 or above is classified as obese, a BMI of 40 or above is classified as extremely obese, and a BMI of 25 to 29.9 is classified as overweight. BMI, while useful for population-level assessments, has well-known limitations at the individual level. It does not account for variations in muscle mass, bone density, and fat distribution, which can lead to misclassification in certain populations, such as athletes or the elderly, nor does it account for ethnic differences in fat accumulation and distribution. Despite these limitations, BMI remains the most accessible and commonly used measure for diagnosing obesity due to its simplicity and ease of use.

In this context, the weakness of BMI is further highlighted by looking at comorbidities and obesity associated health risks in Asian populations, which are more likely to develop abdominal and visceral fat, and have a higher risk of clinical events. Thus, studies like Low et al. (2009) highlight the need for a lower BMI cutoff in for Asian populations compared ot the international BMI cut-off suggested by the WHO. Asian populations have repeatedly shown higher cardiovascular risk factors than Western populations at any given BMI levels (Lau et al. 2009, Weng et al. 2006, Pan et al. 2004, Jafar et al. 2006, Deurenberg et al. 2002).

Classification	**BMI–Non-Asian (kg/m²)**	**BMI–Asian (kg/m²)**
Overweight	25 – 29.9	23 – 24.9
Class I	30 – 34.9	25 – 29.9
Class II	35 – 39.9	30 – 34.9
Class III	$\geq$40	35 – 39.9

Table 1.1: BMI Classifications for Non-Asian and Asian Populations

State-of-the-art measures of body fat adiposity such as underwater weighing, dual-energy x-ray absorptiometry (DEXA) scanning, computed tomography (CT), and magnetic resonance imaging (MRI) are expensive and impractical alternatives to BMI, although more accurate. In addition to these methods, other measures can be used as complementary to BMI to assess

health risks associated with obesity. These include waist circumference, an indicator of abdominal obesity which is associated with higher risk of metabolic implications, and body fat percentage, considered an overall better predictor of visceral fat mass and an a rick factor for cardiovascular diseases, diabetes and metabolic disorders (De Koning et al. 2007, Kapusinac et al. 2017). Finally, measures such as the waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) are emerging indicators of obesity-related health risks rather than waist circumference alone.

1.1.1 Obesity Phenotypes

Obesity is not a homogenous condition, and individuals with the same level of adiposity can exhibit distinct metabolic profiles (Miklishanskaya et al. 2021). This variability has led to the classification of different obesity phenotypes, which provide better insights into the health risks associated with excessive fat accumulation. Vecchié et al. (2018) distinguish between four different phenotypes according to their clinical features:

- **Metabolically healthy obese**. Characterized by BMI>30, low visceral adipose tissue, high lean mass, high cardiorespiratory function, and no metabolic abnormalities.
- **Metabolically obese normal weight**. Characterized by 18,5<BMI<25, high visceral adipose tissue, normal lean mass, low cardiorespiratory function, and metabolic abnormalities.
- **Normal weight obese**. Characterized by 18,5<BMI<25, a fat mass of 30% or more, normal amounts of lean mass, variable cardiorespiratory function and, no metabolic abnormalities.
- **Sarcopenic obese**. Characterized by BMI>30, high visceral adipose tissue, low lean mass, low cardiorespiratory function, and the presence of metabolic abnormalities.

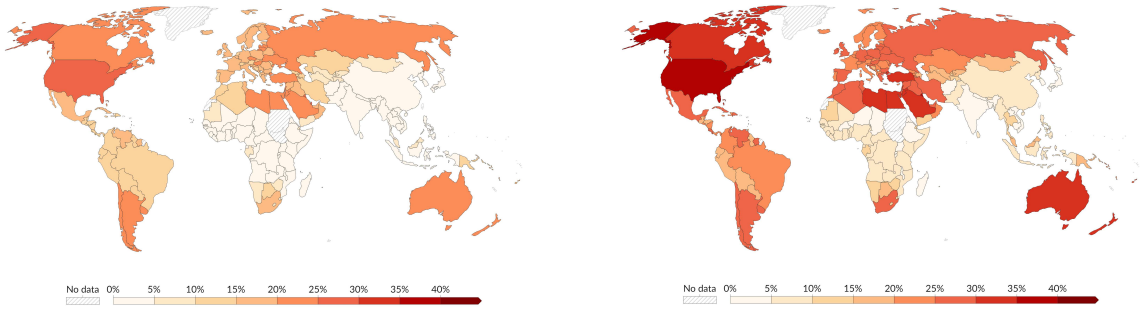
The identification of these phenotypes has illuminated the complexity of obesity and the role fat distribution plays in health outcomes. The data from the observation of different phenotypes highlights an obesity paradox, as it suggests that in certain populations, higher body fat may be associated with better survival outcomes, particularly in cardiovascular conditions. However,

this paradox may be partly explained by the limitations of BMI as a measure of obesity, as it fails to account for variations in fat distribution, lean mass, and other factors (Lavie et al. 2014, Bhaskaran et al. 2014, Dixon et al. 2014, Gruberg et al. 2002, Stokes et al. 2015). Miklishanskaya et al. (2021) highlight that the accumulation of visceral adipose tissue is closely linked to adverse health outcomes, significantly increasing the risk of metabolic disorders such as T2D and cardiovascular disease (Brown et al. 2016, Druzhilov et al. 2015). Moreover, ectopic fat deposition -the abnormal storage of fat in organs like the liver and heart- further raises the likelihood of developing conditions like atherosclerosis (Neeland et al. 2019). These findings suggest that fat distribution, particularly the presence of visceral and ectopic fat, plays a critical role in the heightened health risks associated with obesity and drive the findings related to the existence of different obesity phenotypes.

1.2 Epidemiology of Obesity

The prevalence of obesity has increased dramatically over the past few decades, reaching epidemic proportions worldwide (WHO, 2024). The epidemiology of obesity varies significantly across regions, with higher prevalence observed in high-income countries, particularly in North America, Europe, and parts of the Middle East. However, obesity is also on the rise in low- and middle-income countries, particularly in urban areas, where rapid urbanization, sedentary lifestyles, and dietary transitions toward processed foods are driving the epidemic. Obesity rates also differ by age and gender. In most regions, obesity is more prevalent among middle-aged adults and tends to be higher in women compared to men, although the gender gap varies by region. Children and adolescents have also seen alarming increases in obesity prevalence, which poses significant public health concerns for future generations. Socioeconomic factors further contribute to obesity risk, with lower-income populations often facing higher rates of obesity due to reduced access to healthy food options and opportunities for physical activity.

Figure 1.1 shows the evolution of obesity (BMI$>$30) in adults between 2006 and 2016. A clear upwards trend emerges at first glance, with obesity rates increasing steadily across both men and women over the decade and across geographies. This trend reflects the growing global burden of obesity, particularly in urbanized and industrialized regions. Contributing factors such as sedentary lifestyles, changes in dietary habits toward energy-dense foods, and limited



(a) Share of adults classified as obese, 2000

(b) Share of adults classified as obese, 2016

Figure 1.1: Comparison of the share of adults classified as obese between 2000 and 2016
Source: WHO - Global Health Observatory (2024).

access to healthier options have exacerbated this rise. Between 1990 and 2022, the prevalence of obesity in adults increased in 188 countries according to Robinson et al. (2024), signaling an increase in the burden of obesity driven by a nutrition transition towards calorie dense foods. Globally, obesity increased from 5% in 1980 to 10.1% in 2015 for men, and from 8.9% to 14.8% for women (Chooi et al. 2019). Overall prevalence of obesity remains highest in the Americas and Europe, coupled with a steady increase from 12.9% in 1980 to 28.3% in 2015 for the former, and from 11.8% in 1980 to 19.6% for the latter (Chooi et al. 2019). These figures underscore the urgency of addressing obesity as a public health priority.

1.2.1 Heterogeneity in Obese Populations

Obesity is a highly heterogeneous condition, with variations in its prevalence and trends influenced by factors such as sex, socioeconomic status, geography, ethnicity, and age. While obesity can occur at any age and has risen among both children and adults, it disproportionately affects certain groups. Studies consistently show that women and older adults exhibit higher obesity rates, with the prevalence increasing until around age 80, after which the difference in obesity rates between older and younger adults becomes less pronounced (GBD 2015, Chooi et al. 2019, Hruby et al. 2015, Ogden et al. 2007).

Socioeconomic factors play a significant role in shaping obesity patterns, though the direction and magnitude of these effects vary with the level of economic development. In low-income countries, obesity is often positively correlated with wealth, as individuals in higher socioeconomic brackets have greater access to energy-dense foods (Ogden et al. 2007, Mbogori et al. 2020). Conversely, in middle-income countries more affluent households and those with higher

educational attainment tend to show a greater prevalence of overweight individuals, though exceptions exist such as Colombia where the inverse relationship is observed (Jimenez-Mora et al. 2020). In high-income countries, the link between obesity and socioeconomic status is complex. While obesity rates in men show less defined patterns, women from lower socioeconomic backgrounds are often disproportionately affected due to sociocultural factors that may influence dietary habits and physical activity (Chang et al. 2005, Washington et al. 2023).

Educational attainment also influences obesity trends, though the nature of this relationship remains debated. Some studies suggest that higher levels of education are inversely related to obesity rates, particularly in developed countries, where education may provide greater awareness of healthy lifestyles and access to resources (Hammond et al. 2010, Hagman et al. 2017, French et al. 2018).

Genetics plays a crucial role in obesity, with numerous studies identifying specific genes that influence appetite regulation, fat storage, and energy metabolism. Variants in genes such as FTO and MC4R are associated with increased obesity risk due to their effects on hunger and energy expenditure (Locke et al. 2015, Hägg et al. 2015, Rivera et al. 2017). However, genetics alone does not determine obesity outcomes; the interaction between genetic predisposition and environmental factors, such as diet and physical activity, can either amplify or mitigate this risk.

Psychosocial factors, including stress, depression, and disordered eating, significantly contribute to the development and persistence of obesity. Individuals facing chronic stress or mental health conditions may turn to food for comfort, particularly high-calorie, energy-dense foods, which can exacerbate weight gain. Additionally, socioeconomic stressors such as financial insecurity or social isolation can reduce access to healthy lifestyle choices, further promoting obesity.

Food insecurity has been shown to have a relationship with obesity in women, children and adolescents, while this relationship has not been observed for young adults and the elderly (Carvajal-Aldaz et al. 2022, Farrell et al. 2018). The relationship between food insecurity and obesity is often referred to as the ”food insecurity-obesity paradox.” One hypothesis, known as the insurance hypothesis, suggests that individuals facing food insecurity overconsume calorie-dense foods during periods of availability, in anticipation of future shortages, leading to weight gain (Nettle et al. 2017). In low-income populations, the affordability of high-calorie, low-nutrient foods often exacerbates this issue, as financial constraints limit access to healthier

options (Kowaleski-Jones et al. 2018). The psychological stress associated with food insecurity can also drive overeating as a coping mechanism, further contributing to obesity (Ashe and Lapane 2018, Jokela et al. 2023). In addition, research shows that social support systems may buffer the impact of food insecurity, reducing the likelihood of overeating and promoting healthier food choices (Hernandez et al. 2017).

Studies have shown that obesity can serve as a causal risk factor for depression, with studies suggesting that excess weight can contribute to poor mental health outcomes, particularly depression (Jokela and Laakasuo 2023, Sharafi et al. 2020). A bidirectional relationship runs between the two, as depression can also lead to obesity due to behavioral factors like emotional eating and decreased physical activity, creating a reinforcing cycle. Mannan et al. (2016) finds that depressed individuals had a 37% increase in risk of being obese, and those who were obese had an 18% risk of being depressed, although these reciprocal associations were not found to be significant. Mental health challenges often begin in childhood or adolescence, as research indicates that children with obesity are more likely to develop anxiety and depression, and have higher symptom severity, compounding their risk for poor long-term mental and physical health outcomes (Beltrán-Garrayo et al. 2023).

1.2.2 Pathophysiology of Obesity

The pathophysiology of obesity involves intricate interactions between genetic, hormonal, and environmental factors that disrupt normal metabolic processes. One of the key mechanisms underlying obesity is the dysregulation of energy homeostasis, where the body's systems for regulating hunger, satiety, and energy expenditure become impaired. Hormones such as leptin and ghrelin play pivotal roles in this process. Leptin, produced by adipose tissue, signals the brain to reduce appetite, while ghrelin, secreted by the stomach, stimulates hunger. In individuals with obesity, leptin resistance often develops, impairing the feedback mechanism that normally curbs food intake (Bray 2004).

The expansion of adipose tissue in obesity is not merely a result of excess fat storage but also leads to adipose tissue dysfunction. As adipocytes enlarge, they become metabolically active, secreting proinflammatory cytokines, which contribute to systemic inflammation. This chronic inflammatory state fosters insulin resistance, a key factor in the development of T2D and other metabolic disorders. Additionally, adipokines, signaling molecules released by adipose tissue,

are altered in obesity, with increased production of proinflammatory adipokines and decreased levels of anti-inflammatory ones like adiponectin (Bray 2004, Saltiel and Olefsky 2017).

This inflammatory state promotes hormonal imbanalances, which affect glucose metabolism leading to insulin resistance. In turn, elevated insulin levels contribute to further fat storage, particularly in visceral adipose tissue, worsening metabolic health. Excess visceral fat is associated with an increased risk of cardiovascular diseases as it promotes lipid abnormalities, hypertension, and atherosclerosis (Bray 2004). The accumulation of fat in non-adipose tissues, such as the liver (leading to non-alcoholic fatty liver disease, NAFLD) and muscles, further disrupts metabolic homeostasis, contributing to diseases like T2D and cardiovascular conditions.

1.2.3 The link between obesity and metabolic diseases

The current obesity pandemic is the leading cause of soaring rates of metabolic diseases such as diabetes, cardiovascular disease, hypertension and non-alcoholic hepatosteatosis (Cao, 2014, Eckel et al. 2005). The inflammatory and metabolic disturbances triggered by obesity set the stage for a range of chronic diseases. Elevated levels of free fatty acids and ectopic fat deposition in organs like the liver impair their function, promoting insulin resistance and contributing to the pathogenesis of T2D and progressive conditions such as NAFLS, MASH and MASLD. Inflammation within adipose tissue further drives systemic insulin resistance, linking obesity to an increased risk of cardiovascular disease, certain cancers, and other chronic conditions (Bray 2004, Saltiel and Olefsky 2017, Cao 2014, Eckel et al. 2005).

Therefore, the treatment of obesity is inextricably linked to the management of metabolic disorders, given that obesity is a driving factor behind conditions like T2D, dyslipidemia, and hypertension. By addressing obesity, many of the metabolic abnormalities associated with excess weight, particularly insulin resistance and systemic inflammation, can be improved or even reversed (Bray 2004, Sjöström et al. 1997). Weight loss, achieved through lifestyle interventions, pharmacotherapy, or surgery, has been shown to significantly reduce the risk of developing T2D and improve cardiovascular outcomes (Lean et al. 2018) and can even lead to remission (Kwee et al. 2021, Sjöström et al. 1997).

The literature on the risk reduction effect of weight loss sheds light on the potential benefits of pharmacological interventions in the treatment of obesity. Aucott et al. (2004) and Norris et al. (2005) find a negative association between weight loss and risk of developing diabetes

in individual with either a family history of developing diabetes or impaired glucose tolerance, and an overall improvement in the metabolic handling of glucose in those with T2D after weight loss. Weight loss can also aid in the remission of metabolic syndrome (Lundgren et al. 2009).

This chapter highlighted obesity as a complex and multifactorial disease which plays a pivotal role in the development and progression of various comorbid diseases. Its pathophysiology is characterized by complex interactions between genetic, hormonal, and environmental factors, which all contribute to its persistence and association with conditions such as T2D, cardiovascular disease, hypertension and metabolic conditions such as NAFLD, MASH and MASLD. Despite the limitations of traditional metrics like BMI, advancements in understanding obesity phenotypes and the critical role of fat distribution provide deeper insights into its diverse health impacts. Tackling obesity requires a multifaceted approach that goes beyond simple weight reduction, addressing underlying systemic inflammation, hormonal imbalances, and insulin resistance to mitigate its associated risks. Thus, combating the obesity epidemic is not just about managing body weight, but about understanding and addressing the broader metabolic dysfunctions associated with it.

The following chapter will explore the various management and treatment strategies available to combat the obesity epidemic on an individual level. From lifestyle intervention and surgical options, to the introduction of pharmacological approaches, the treatment of obesity offers is multifaceted and heterogeneous, as the disease needs to address not only weight reduction but also the broader dysfunctions connected to it.

2 The Obesity Treatment Landscape

Obesity prevalence is expected to continue to increase in the future. By 2030, the number of obesity patients worldwide is expected to be over 1 billion (CDC - Overweight and Obesity), with persistently high unmet need. Combating obesity has long been one of medicine's greatest challenges, with approaches evolving significantly throughout history. Early efforts focused primarily on dietary restrictions and increased physical activity, but as the understanding of obesity's complexity deepened so did the strategies for its management. Over time treatment paradigms expanded to include behavioral therapy, pharmacological interventions and, in more severe cases, bariatric surgery. Today, the landscape of obesity management is more structured and nuanced, offering a multi-disciplinary approach that targets not only weight reduction but also the underlying metabolic dysfunctions. In particular, recent years have seen the rise of novel pharmacotherapies such as GLP-1 receptor agonists under brand names like Wegovy, Ozempic and Mounjaro, which have shown impressive clinical trial and real world results.

The current chapter offers a landscape view of the main treatment alternatives to address obesity, spanning from lifestyle interventions to surgical interventions, with particular focus on their effectiveness and sustainability. Most importantly, a section will focus on Glucagon-like Peptide-1 receptor agonists (GLP-1 RAs), which represent the main innovation in anti-obesity medication options in recent decades, and are the main focus of this work. The aim of this chapter is to provide a clinical and treatment-based perspective on obesity treatment, leaving an in-depth market analysis of GLP-1 RAs to the following chapter.

In the following sections, I will discuss the various treatment options for obesity in the order that aligns with their placement along the line of treatment. This progression begins with lifestyle interventions, followed by pharmacological therapies, and advances to more intensive approaches such as device-based therapies and surgical interventions which are reserved for the more severe cases. This structure reflects the standard approach to obesity management, where

treatment becomes progressively more invasive based on the patient's needs and response to earlier interventions. For a visual representation of how these options are organized along the treatment pathway, please refer to Figure 2.1.

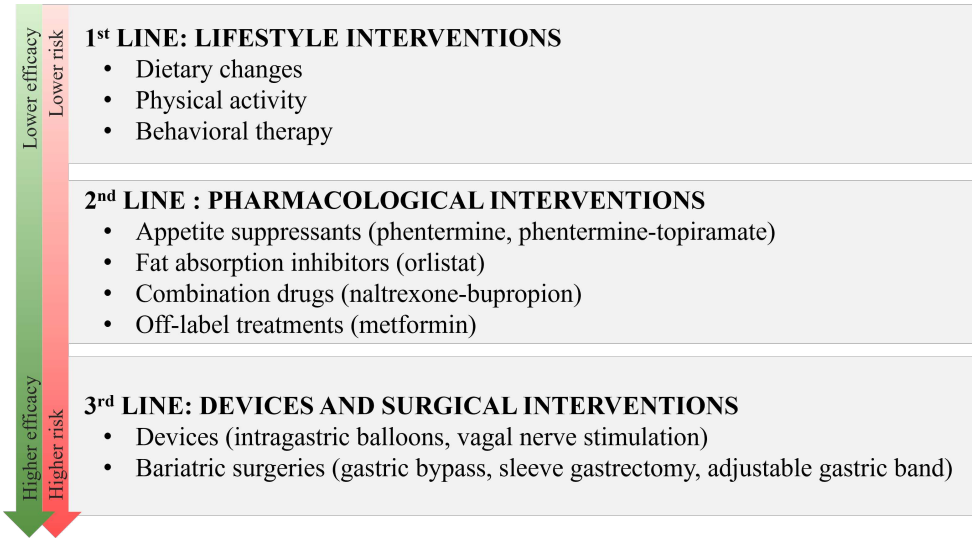


Figure 2.1: Progressive Treatment Options for Obesity Management (excl. GLP-1 RAs)

Source: NICE, "Obesity: identification, assessment and management." (2014).

2.1 Lifestyle Interventions

Lifestyle changes represent a cornerstone of obesity management, focusing on long-term behavior modification in diet, physical activity and daily habits. These interventions are generally considered the first line of treatment for overweight and obese individuals, and can be roughly categorized into dietary changes, physical activity and behavioral therapy (Wadden et al. 2020).

Dietary modifications aim at producing a sustained caloric deficit to promote weight loss through calorie restriction, low-carbohydrate diets, and intermittent fasting. Calorie restriction and structured dietary programs can lead to sustained weight loss, especially when combined with behavioral support. Although short term weight loss strategies have improved over previous decades, long-term weight management has been much less successful (Jeffery et al. 2000). Additionally, while research has shown that caloric restriction leads to fat loss, it has also highlighted the potential for muscle mass loss, necessitating careful planning to avoid adverse metabolic effects (Cava et al. 2017, Santanasto et al. 2011).

Regular physical activity is another critical element in lifestyle interventions for managing

obesity and metabolic conditions. Exercise alone, while beneficial for overall health, often results in modest weight loss compared to diet. Regular activity can not only increase the caloric expense but also combat the muscle loss associated with dietary interventions (Cava et al. 2017).

Behavioral therapy improves weight loss outcomes by addressing the underlying behaviors and psychological factors contributing to obesity, such as disordered eating (Castelnuovo et al. 2017, Grilo et al 2011). When combined with diet and exercise, cognitive-behavioral therapy (CBT) can increase the success rate of weight loss efforts. Long term success is highly correlated with sustained behavioral change, so that practicing the techniques learned in behavioral therapy (self-monitoring, setting realistic goals, developing coping strategies for triggers) can help maintain weight loss and prevent weight regain. Additionally, patient characteristics such as being male, older, having cardiometabolic comorbidities and limited fat intake were significantly associated with weight loss (Chopra et al. 2020).

Intensive lifestyle interventions can be successful for short-term weight loss, with dramatic improvements in patients' lives. Studies have shown the positive impact of dramatic lifestyle changes on diabetes control, depression, sleep apnea, incontinence, healthcare use and costs (Wing et al. 2021). Composite indices such as the presence of multimorbidity, geriatric symptoms and disability free life years have also shown improvements in response to intensive lifestyle interventions. At the same time, other important facets of obesity such as cardiovascular morbidity and mortality, as well as cancer and cognitive function, and impairment have shown no significant changes; additionally, weight loss was associated with loss of lean body mass and an increase in frailty fractures (Wing et al. 2021).

2.2 Pharmacological Treatments

Across all pharmacological interventions for obesity, a common theme is the importance of combining medication with lifestyle modifications, such as diet and exercise, to maximize and sustain weight loss, as well as prevent negative side effect of rapid weight loss such as diminishing lean mass. While these treatments offer varying mechanisms of action, they share certain limitations, including potential side effects and contraindications that must be carefully managed. Additionally, most medications show moderate efficacy, often leading to weight re-

ductions of around 5-10% in excess of placebo when used alongside lifestyle changes, with varying impacts on metabolic health.

2.2.1 Phentermine

Pharmacological treatments that suppress appetite, such as phentermine and the combination drug phentermine-topiramate, represent a second-line approach to managing obesity. Phentermine, sold under the brand names such as Adipex-P and as a generic medication, is a sympathomimetic oral treatment that has demonstrated short-term effectiveness in weight management and is FDA-approved. As noted by May et al. (2020), phentermine is an amphetamine-like drug that promotes weight loss by stimulating the sympathetic nervous system, which increases resting energy expenditure and reduces food intake. However, it is contraindicated for patients with a history of substance abuse, cardiovascular disease, hyperthyroidism, glaucoma, or pregnancy. Phentermine also has significant drug-drug interactions, particularly with monoamine oxidase inhibitors (MAOIs), which are commonly used to treat mood disorders, obsessive-compulsive disorder, Parkinson's disease, and eating disorders.

2.2.2 Phentermine-topiramate

Phentermine is also marketed in combination with topiramate under the brand name Qsymia or Qsiva by Vivus, and is a combination therapy which has weight-reducing effects, potentially through mechanisms such as taste aversion and appetite suppression. However, topiramate carries teratogenic risks, making it unsuitable for use in pregnancy (May et al. 2020, FDA, Smith et al. 2013, Cosentino et al. 2011). In terms of long-term efficacy, Garvey et al. (2012) analyzed data from the SEQUEL trial, a follow-up to the CONQUER trial, which assessed the sustained impact of phentermine-topiramate at different dosages. At 108 weeks, patients achieved a weight reduction of 9.3-10.5%. These findings align with earlier results from the CONQUER trial (Gadde et al. 2011), which also noted improvements in cardiovascular health, metabolic markers, and comorbid conditions.

2.2.3 Orlistat

Another second-line pharmacological treatment for obesity is the fat absorption inhibitor orlistat, sold under the brand name Xenical by Roche and as a generic. Currently, it is approved in the US and EU as an obesity treatment. Orlistat works by inhibiting pancreatic and gastric lipases, the enzymes responsible for breaking down dietary fat, thereby reducing fat absorption by around 25-30% (May et al. 2020, Apovian et al. 2015). Studies showed that after 1 year of treatment, patients on orlistat lost around 9% of body weight compared to 5.8% in placebo (Heck et al. 2000). While effective, orlistat is commonly associated with gastrointestinal side effects such as oily stools, flatulence, and frequent bowel movements, which can impact adherence. Its long-term use is generally well-tolerated, although vitamin deficiencies (particularly fat-soluble vitamins A, D, E, and K) may occur due to the reduced fat absorption, necessitating supplementation (Heck et al. 2000). Drug-drug interactions are not significant although possible due to inhibited resorption in the intestine (May et al. 2020).

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis. Additionally, caution should be exercised in individuals with kidney disease, as orlistat can increase the risk of oxalate-induced kidney stones. Despite these concerns, studies like the XENDOS trial show that long-term use of orlistat (over four years) not only promotes weight loss but also reduces the risk of developing T2D in obese patients by 37% (Torgerson et al. 2004).

2.2.4 Naltrexone-bupropion

A fourth pharmacological approach for obesity management is the combination of naltrexone-bupropion, which targets appetite control and is currently approved in the US under the name Contrave, and in the EU under the brand Mysimba. Naltrexone, an opioid receptor antagonist, is typically used to treat alcohol and opioid dependence, while bupropion, a dopamine and norepinephrine reuptake inhibitor, is prescribed for depression and smoking cessation. When combined, these drugs work synergistically to reduce cravings and control eating behavior, particularly for individuals who struggle with food addiction and emotional eating (Greenway et al. 2010). Taking naltrexone-bupropion over 12 months has been associated with weight loss of 4.8% in excess of diet and lifestyle alone (Greenway et al. 2010, Apovian et al. 2015).

Naltrexone-bupropion has been shown to improve several metabolic markers, including glycemic control and cholesterol levels, making it an attractive option for individuals with metabolic syndrome. It is contraindicated in individuals with uncontrolled hypertension, seizure disorders, or a history of anorexia or bulimia, as bupropion lowers the seizure threshold. Moreover, it should not be used in patients who are dependent on opioids, as naltrexone blocks opioid receptors, potentially precipitating withdrawal symptoms (Greenway et al. 2010).

2.2.5 Metformin

Finally, some patients may be treated with off-label metformin to aid in weight loss. Although primarily prescribed for the treatment of T2D, metformin is sometimes used off-label for weight management, particularly in individuals with insulin resistance or prediabetes. Metformin works by reducing hepatic glucose production and improving insulin sensitivity, which indirectly supports weight loss through better metabolic control (Knowler et al. 2002). Unlike other pharmacological treatments, metformin does not directly suppress appetite or reduce fat absorption, but it can lead to modest weight reduction by stabilizing blood sugar levels and reducing hunger in some patients.

Clinical studies, such as the Diabetes Prevention Program (DPP), have shown that patients treated with metformin experience modest weight loss of 2-4% over 1-2 years (DPP Research Group, 2002). This effect, while less pronounced than other obesity medications, can be sustained long term, particularly when combined with lifestyle changes like diet and exercise. Metformin's most significant benefit lies in its ability to prevent weight regain and improve insulin sensitivity, making it especially useful for individuals at risk of developing T2D. Metformin is contraindicated in individuals with severe kidney disease or significant liver dysfunction (Saenz et al. 2005).

In addition to the pharmaceutical options listed above, Sanorex (mazindol), sponsored by Pfizer, and Oblean (cetilistat), sponsored by Takeda, are approved in Japan. Finally, the combination of benzphetamine, phendimetrazine, and diethylpropion is another sympathomimetic drug approved by the FDA for the US market.

2.3 Pharmaceutical Innovations: GLP-1 RAs

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a transformative class of treatments in the fight against obesity and metabolic disorders. Originally developed for managing T2D, these medications—such as liraglutide (Saxenda) and semaglutide (Wegovy, Ozempic)—have demonstrated significant efficacy in weight management by enhancing insulin secretion, reducing appetite, and slowing gastric emptying. GLP-1 RAs mimic the incretin hormone GLP-1, which regulates glucose metabolism, reduces hunger, and delays gastric emptying, resulting in enhanced satiety and controlled appetite. This mechanism positions GLP-1 RAs as particularly effective for long-term weight loss, especially in patients with metabolic comorbidities such as diabetes.

The first GLP-1 RA approved specifically for obesity was Saxenda (liraglutide), granted FDA approval in 2014 and EMA approval in 2015 for use in patients with a body mass index (BMI) classified as obese and at least one comorbid condition. Following this, the FDA extended approval to adolescents aged 12 and older in 2020, with the EMA following suit in 2022. Semaglutide, under the brand name Wegovy, became the second GLP-1 RA approved for obesity management, receiving FDA approval in June 2021 and EMA approval in January 2022. Like its predecessor, Wegovy showed superior weight loss efficacy compared to older pharmacological treatments in several clinical trials.

GLP-1 RAs' success in obesity treatment was bolstered by their off-label use for weight loss even before specific approvals. For instance, Ozempic (semaglutide) and Rybelsus (oral semaglutide) were initially approved for diabetes management but gained rapid off-label adoption for obesity treatment due to their significant weight loss effects. Tirzepatide (Zepbound), a dual GLP-1 and GIP receptor agonist, was recently approved by the FDA for obesity management in November 2023. Like Saxenda and Wegovy, Zepbound had already been available under the name Mounjaro for treating T2D, further reflecting the shift of GLP-1 RAs from diabetes therapies to mainstream obesity management.

These GLP-1 RAs have reshaped the landscape of obesity treatment by offering unprecedented long-term weight loss potential and metabolic improvements. They represent a promising frontier in addressing the global obesity epidemic, particularly in patients with metabolic disorders such as T2D. As these agents become more accessible, the market for GLP-1 RAs is

Compound	Trial Acronym	Phase	Sponsor	Indications	Comparators
semaglutide	PIONEER 1-12, PIONEER PLUS	Phase III	Novo Nordisk	Diabetes Mellitus Type 2	Placebo, dulaglutide, sitagliptin, empagliflozin, liraglutide
semaglutide	SELECT	Phase III	Novo Nordisk	Overweight, obesity	Placebo
semaglutide	STEP 1-8, STEP'HF-pEF	Phase III	Novo Nordisk	Overweight, obesity, metabolism and nutrition disorder	Placebo, liraglutide
semaglutide	SUSTAIN, SUSTAIN 1-11, SUSTAIN FORTE	Phase III	Novo Nordisk	Diabetes Mellitus Type 2	Placebo, sitagliptin, liraglutide, insulin aspart, insulin glargine, dulaglutide, canagliflozin, DPP-4 inhibitor, exenatide
liraglutide	ADJUNCT 1-2	Phase III	Novo Nordisk	Diabetes Mellitus Type 1	Placebo
insulin degludec + liraglutide	DUAL 1-8	Phase III	Novo Nordisk	Diabetes Mellitus Type 2	Placebo, insulin glargine, insulin aspart, liraglutide, exenatide
liraglutide + metformin	Ellipse	Phase III	Novo Nordisk	Diabetes Mellitus Type 2	Placebo, metformin
liraglutide	LEAD 2, 6, LEADER	Phase III	Novo Nordisk	Diabetes Mellitus Type 2	Placebo, exenatide, metformin, glimepiride
liraglutide	SCALE IBT, SCALE INSULIN	Phase III	Novo Nordisk	Obesity	Placebo, CMS Intensive Behavioral Therapy
tirzepatide	SURMOUNT 1-4, SURMOUNT CN, SURMOUNT J	Phase III	Eli Lilly	Obesity, Overweight, Diabetes Mellitus Type 2, Metabolism and nutrition disorder	Placebo
tirzepatide	SURPASS 1-6, J	Phase III	Eli Lilly	Diabetes Mellitus Type 2	Placebo, semaglutide, insulin degludec, insulin glargine, insulin lispro
exenatide	DURATION-NEO-1, 2	Phase III	AstraZeneca	Diabetes Mellitus Type 2	Placebo, sitagliptin
dulaglutide	AWARD 1-11, AWARD-CHN 1-3, AWARD-JPN, AWARD-PEDS	Phase III	Eli Lilly	Diabetes Mellitus Type 2, Chronic Kidney Disease, Metabolic disease, Endocrine system disease	Placebo, metformin, SGLT2 inhibitor, liraglutide, insulin glargine, insulin lispro, glimepiride, sulfonylureas, oral antihyperglycemics

Table 2.1: Selection of Completed Clinical Trials For Key GLP-1 RAs

Source: clinicaltrials.gov.

expected to expand significantly, with continued innovation and pipeline developments in the near future. For further analysis of ongoing clinical trials and the future market outlook, see the next chapter. A selection of key completed trials is provided in Table 2.1.

In this section, I will explore the clinical evidence supporting the use of several key GLP-1 receptor agonists for obesity and metabolic disorders. Specifically, I will discuss the more promising drugs in the GLP-1 RAs class, namely semaglutide, liraglutide, tirzepatide, and dulaglutide. For each drug, I will review the most relevant trial results, mainly focusing on major Phase 3 studies. These trials provide valuable insights into the efficacy, safety, and clinical applicability of these treatments in managing obesity and related comorbidities.

2.3.1 Semaglutide

Semaglutide, marketed as a Wegovy, is a GLP-1 receptor agonist developed by Novo Nordisk, has been extensively studied for its effects on overweight, obesity, and T2D. Its pivotal role in weight management has been demonstrated through two key Phase 3 clinical trials: the STEP (Semaglutide Treatment Effect in People with Obesity) and SUSTAIN (Semaglutide Unabated Sustainability in Treatment of T2D) programs. These trials established semaglutide's significant efficacy in promoting weight loss, improving glycemic control, and reducing cardiovascular risk factors in individuals with obesity and T2D (Bergmann et al. 2023, Wadden et al. 2021, Rubino et al. 2021).

The STEP clinical trials evaluated once-weekly subcutaneous semaglutide 2.4 mg against placebo and liraglutide over 68-104 weeks in individuals with obesity (BMI $\geq$ 30) or overweight (BMI $\geq$ 27 with at least one comorbidity). Background treatments included lifestyle interventions such as a 500 kcal/day caloric deficit and intensive behavioral therapy. Results demonstrated an impressive mean weight loss of 14.9% to 17.4% after 68 weeks in participants without T2D. Additionally, 69%-79% of participants treated with semaglutide experienced at least a 10% weight loss, compared to 12%-27% in the placebo group. Across all trials, semaglutide also improved cardiovascular and metabolic risk factors, further highlighting its therapeutic potential in obesity management (Bergmann et al. 2023, Wadden et al. 2021, Rubino et al. 2021).

The SUSTAIN clinical trials have investigated the effect of semaglutide on patients with T2D in randomized, parallel-grup, multicentre, controlled trials. Comparators were placebo (SUSTAIN 1, 2, 5), sitagliptin (SUSTAIN 2), exenatide (SUSTAIN 3), insulin glargine (SUSTAIN 4) and dulaglutide (SUSTAIN 7). Across these trials, semaglutide demonstrated glycaemic control properties, the ability to control body weight, improve blood pressure, pulse and lipid parameters, and last but not least improve cardiovascular endpoints such as cardiovascular death, ischaemic stroke (fatal and non-fatal) in diabetic individuals (Aroda et al. 2019).

Regarding safety and tolerability, semaglutide has shown a generally favorable profile. The most common adverse events are gastrointestinal, including nausea, vomiting, diarrhea, and constipation, particularly during the early stages of treatment. These side effects are dose-dependent and tend to subside as patients acclimate to the medication. More severe but rare

risks include pancreatitis, gallbladder issues, and in some cases, an increase in heart rate in patients with pre-existing conditions. The FDA has issued a black box warning for thyroid C-cell tumors and multiple endocrine neoplasia (MEN-2), prompting prescriber to exercise caution when providing the medication and monitoring patients. Overall, semaglutide is considered well-tolerated, with side effects that are generally manageable for most patients (Bergmann et al. 2023, Wadden et al. 2021, Rubino et al. 2021, Aroda et al. 2019).

Currently, once-weekly subcutaneous semaglutide 2.4 mg is approved in Canada, Europe, the UK, and the USA as an adjunct to lifestyle interventions for chronic weight management in obese adults (BMI $\geq$ 30) or overweight adults (BMI $\geq$ 27) with at least one comorbid condition. To minimize gastrointestinal side effects, the treatment is initiated at a lower dose of 0.25 mg once weekly, with gradual monthly escalation to the 2.4 mg target dose. In cases of adverse events during dose escalation, temporary dose de-escalation or interruption is recommended (Novo Nordisk 2021, EMA 2024, Health Canada 2022).

2.3.2 Liraglutide

Liraglutide, another GLP-1 RA developed by Novo Nordisk, was initially approved for the treatment of T2D under the brand name Victoza. It later gained approval for chronic weight management as Saxenda, demonstrating efficacy in reducing body weight and improving metabolic outcomes in individuals with obesity or overweight with comorbid conditions. Liraglutide's efficacy in weight management was primarily demonstrated through the SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence) trials, a series of Phase 3 studies evaluating its effects on weight loss in individuals with obesity or overweight (Davies et al. 2018, Verges et al. 2017, Pi-Sunyer et al. 2015).

The SCALE placebo-controlled trials focused on obese adults (BMI $\geq$ 30) or overweight adults (BMI $\geq$ 27) with comorbid dyslipidemia or hypertension, for an observational period of 56 weeks. Liraglutide was administered in once-daily subcutaneous injections of 3mg, with both placebo and treatment groups receiving counseling on lifestyle modifications. For the treated individuals, weight loss of more than 10% was observed in 33.1% of patients, as opposed to only 10.6% of the placebo group (Davies et al. 2018, Verges et al. 2017, Pi-Sunyer et al. 2015).

Liraglutide has demonstrated a generally favorable safety profile, with the most common

reported side effects being gastrintestinal events such as nausea, vomiting, diarrhea, and constipation, which tend to be most pronounced during the initial stages of treatment. The FDA issued a black box warning for thyroid tumors and acute pancreatitis, meaning there is a significant risk for these conditions associated with taking medications such as Saxenda, and that prescripers must exercise caution when prescribing a monitoring patients. As with other treatments in this class, the adverse events tend to appear in the initial phases of treatment (Davies et al. 2018, Verges et al. 2017, Pi-Sunyer et al. 2015).

Currently, liraglutide is approved for the treatment of obesity in the US and the EU. It was approved by the FDA in 2014 and by the EMA in 2015 for adults with BMI $\geq$ 30 or BMI $\geq$ 27 and at least one comorbid condition (FDA 2014, EMA 2018).

2.3.3 Tirzepatide

Tirzepatide, developed by Eli Lilly, is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist that has garnered significant attention for its potent effects in managing both T2D and obesity. It represents a new class of treatment, combining the mechanisms of two incretin hormones, which enhances its ability to regulate blood sugar levels and promote substantial weight loss. The SURMOUNT (Tirzepatide in Obesity) and SURPASS (Tirzepatide in T2D) clinical trials have been pivotal in demonstrating tirzepatide's efficacy, positioning it as one of the most promising therapeutic options for patients with metabolic disorders. The SURMOUNT trials focused on evaluating tirzepatide's efficacy for weight management in individuals with obesity or overweight, using placebo as the primary comparator over treatment durations of up to 72 weeks. In contrast, the SURPASS trials assessed tirzepatide in patients with T2D, comparing it to GLP-1 RAs (like semaglutide), insulin therapies, and other antidiabetic agents over a similar period. Results from Phase 3 trials have shown that tirzepatide offers superior weight loss outcomes compared to existing GLP-1 receptor agonists, with additional benefits in glycemic control and cardiovascular risk reduction, with benefits increasing with dosage (Aronne et al. 2024, Garvey et al. 2023, Wadden et al. 2023, Jastreboff et al. 2022).

The SURMOUNT trials were Phase 3, randomized, placebo-controlled trials with obese, obese patients with diabetes, and weight loss maintanence populations with durations of up to 72 weeks. Across trials, participants were administered doses of 5 mg, 10 mg and 15 mg, or

placebo. Results demonstrated substantial and sustained reductions in weight. Patients on 5 mg lost 15.5% of body weight, patients on 10 mg lost 12.8-19.5% and patients on 15 mg lost 14.7-20.9%, as opposed to 3.1% in the placebo group (Garvey et al. 2023, Jastreboff et al. 2022). Long-term maintenance of weight loss with tirzepatide was explored in SURMOUNT 4, which confirmed that treatment interruption led to substantial weight regain, whereas continued treatment boosted weight loss by an additional 5.5% between weeks 36 to 88 (Aronne et al. 2024).

The SURPASS trials focused on adults with T2D, and lasted between 40-52 weeks, comparing tirzepatide to other treatments including semaglutide, insulin glargine, and insulin degludec. Across trials, tirzepatide consistently demonstrated superior efficacy in reducing HbA1c levels and promoting weight loss compared to its comparators. Patients achieved HbA1c reductions of up to 2.4% and weight loss of up to 11-13% depending on the dose. The SURPASS trials demonstrated tirzepatide's efficacy in managing T2D, with mean change from baseline in glycated hemoglobin level of -2.01%, -2.24%, and -2.30% for 5 mg, 10 mg, and 15 mg of tirzepatide, compared to -1.86% with semaglutide (Frias et al. 2021). Additionally, tirzepatide at all doses was found to be superior to insulin degludec (Ludvik et al. 2021).

Tirzepatide demonstrated a generally favorable safety profile across both the SURMOUNT and SURPASS trials, although like other incretin-based therapies, it is associated with dose-dependent gastrointestinal side effects. The most commonly reported adverse events were nausea, vomiting, diarrhea, and constipation, particularly during the early stages of treatment and when escalating to higher doses. These side effects were generally transient and diminished over time. In patients with T2D, hypoglycemia was more likely to occur when tirzepatide was used in combination with insulin or sulfonylureas.Overall, tirzepatide was considered safe and well-tolerated, with a risk-benefit profile comparable to or better than existing therapies for diabetes and obesity, particularly given its significant efficacy in both weight loss and glycemic control (Frias et al. 2021, Ludvik et al. 2021, Garvey et al. 2023).

Tirzepatide was approved for the treatment of diabetes in the US, EU, Canada and Australia in 2022. The FDA considers it a first-in-class medication, and expanded its label to include weight loss in 2023, followed by the UK (FDA 2022, gov.uk 2023, Therapeutic Goods Administration 2022, EMA 2022).

2.3.4 Dulaglutide

Dulaglutide, marketed as Trulicity by Eli Lilly, is a GLP-1 receptor agonist designed for once-weekly administration to manage T2D and improve metabolic outcomes. Its long-acting formulation enhances patient adherence by providing a convenient dosing schedule. The efficacy and safety of dulaglutide were evaluated in a series of Phase 3 clinical trials known as the AWARD (Assessment of Weekly Administration of Dulaglutide) trials. These trials compared dulaglutide to a range of diabetes treatments, including placebo, metformin, insulin glargine, and other GLP-1 receptor agonists, across diverse populations of patients with T2D.

The AWARD trials demonstrated dulaglutide's consistent efficacy in improving glycemic control and promoting modest weight loss in patients with T2D, although its weight loss effects are not as pronounced as other GLP-1 receptor agonists like semaglutide. Across the AWARD trials, patients experienced reductions in body weight ranging from 1.3 to 4.7 kg, with the higher doses of dulaglutide achieving the most significant weight reductions (Dungan et al. 2014, Frias et al. 2021, Dungan et al. 2016).

Similarly to previously discussed GLP-1s, dulaglutide demonstrated a generally favorable safety profile, with the most common adverse events being gastrointestinal (nausea, vomiting, diarrhea, abdominal discomfort), at the beginning of treatment, and at higher doses (Dungan et al. 2014; Frias et al. 2021).

Currently, dulaglutide is approved in the US for the treatment of adverse cardiovascular events in adults with T2D and a histor of cardiovascular disease or multiple cardiovascular risk factors (Eli Lilly, 2020). In the EU, it is approved for the treatment of T2D, particularly in combination with other diabetes treatments, and for reducing cardiovascular risks in Type 2 diabetic individuals with established cardiovascular disease (EMA, 2014).

2.4 Surgical Interventions

Bariatric surgery is a crucial intervention for obesity treatment, particularly for severely obese individuals who have not achieved significant weight loss through lifestyle modifications or pharmacotherapy. It is generally considered the last line of treatment after less invasive methods have failed, especially for patients with severe obesity (BMI ≥ 40) or those with a BMI $\geq$

35 accompanied by comorbid conditions such as T2D, obstructive sleep apnea, or hypertension (Schroeder et al. 2011). Surgical options include Roux-en-Y Gastric Bypass (RYGB), Sleeve Gastrectomy (SG), and Adjustable Gastric Banding (AGB) (ASMBS, 2021). Although effective, these procedures are invasive and carry inherent risks, making careful patient selection and a lifelong commitment to lifestyle modifications essential to maximize safety and long-term success. The ideal candidates for bariatric surgery are individuals with severe obesity and related comorbidities that could improve with weight loss, those who have unsuccessfully attempted weight loss through non-surgical methods, those who do not have contraindications such as severe cardiovascular disease or end-stage organ failure, and those committed to long-term follow-up care and behavioral changes.

2.4.1 Roux-en-Y Gastric Bypass

Roux-en-Y Gastric Bypass (RYGB) is one of the most commonly performed bariatric procedures worldwide and can be considered the "gold standard" for surgical weight loss interventions (ASMBS 2021). The procedure is both restrictive and malabsorptive, meaning it reduces the stomach's capacity and alters the digestive process to decrease nutrient absorption (Schroeder et al. 2011).

RYGB results in a significant reduction in the volume of food that can be ingested, as well as a decrease in caloric and nutrient absorption. The procedure is typically performed laparoscopically, which minimizes recovery time and reduces the risks associated with open surgery (Nguyen et al. 2009). During the surgery, the stomach is divided into two parts: a small upper pouch (approximately 15-30 mL in volume) and a larger remnant stomach (ASMBS, 2021). The small pouch is connected to the jejunum, forming the "Roux limb," while the duodenum and initial segment of the jejunum are bypassed, creating a Y-shaped configuration (Pories et al. 2008). The combination of gastric restriction and malabsorption leads to substantial weight loss and metabolic improvements, particularly for patients with obesity-related comorbidities.

RYGB has demonstrated significant weight loss outcomes, with patients typically losing 60-80% of their excess body weight within the first 12-18 months post-surgery (ASMBS 2021, Pories et al. 2008). As is expected in obese patients who experience significant weight loss, RYGB is associated with remission or improvement of comorbidities such as T2D, hypertension, and dyslipidemia (ASMBS 2021, Schauer et al. 2017).

Despite impressive weight loss, RYGB is not without risks. Short-term complications include anastomotic leaks, infections, and venous thromboembolism (ASMBS 2021, Nguyen et al. 2009). Long-term complications can involve nutritional deficiencies, such as vitamin B12, iron, calcium, and fat-soluble vitamins, due to the malabsorptive component of the surgery (Schroeder et al. 2011). Dumping syndrome, characterized by rapid gastric emptying leading to nausea, vomiting, and diarrhea, is another potential complication that requires dietary management (Rosenthal et al. 2010). As a consequence, careful patient selection and lifelong monitoring are crucial to mitigate risks.

RYGB is one of the most effective bariatric procedures for achieving and maintaining long-term weight loss. After 12 months, patients may lose as much as 77% of excess weight. Five years after surgery, patients maintain around 50% of weight loss (ASMBS 2021, Schauer et al. 2017). The procedure's effects on appetite regulation, through changes in gut hormones such as ghrelin and GLP-1, are thought to contribute to its sustained efficacy (Cummings et al. 2012). Cummings et al. (2012) identify seven weight-independent mechanisms of metabolic surgery, namely: changes in gut hormones such as increase GLP-1 secrestion (and hence, insulin) and sometimes compromised secretion of pro-diabetes peptide ghrelin, improved bile acid signaling, improved glucose metabolism, increased insulin sensitivity through neural and humoral pathways, reduced glucose transport, reduced branched-chain aminoacids, and alterations in gut microbiota. Nevertheless, successful long-term outcomes depend heavily on ongoing lifestyle modifications, including dietary adjustments, physical activity, and behavioral support.

2.4.2 Sleeve Gastrectomy

Sleeve Gastrectomy (SG) is another widely performed bariatric procedure that involves the removal of approximately 75-80% of the stomach, leaving a tubular "sleeve" that limits food intake (Rosenthal et al. 2010). Unlike RYGB, SG is purely restrictive, meaning that it primarily works by reducing the volume of the stomach without altering the nutrient absorption process, making it an attractive option for patients concerned with malabsorption in RYGB (ASMBS, 2021). SG is usually performed laparoscopically and is considered a less complex procedure compared to RYGB (Rosenthal et al. 2010).

The weight loss outcomes of SG are comparable to RYGB, with patients typically achieving 50-70% of their excess body weight loss within the first two years (Peterli et al. 2013). Although

less so than RYGB, SG is effective in improving obesity-related conditions such as T2D and hypertension (Lee et al. 2011). However, unlike RYGB, SG does not involve a bypass of the intestines, which reduces the risk of nutritional deficiencies (Rosenthal et al. 2010, Schroeder et al. 2011).

Potential complications of SG include staple line leaks, gastroesophageal reflux disease, and, in some cases, the development of vitamin and mineral deficiencies (Hutter et al. 2011). Although the risk of severe nutritional deficiencies is lower than with RYGB, patients must still undergo lifelong nutritional monitoring and supplementation.

2.4.3 Adjustable Gastric Banding

Adjustable Gastric Banding (AGB) is a less commonly performed bariatric procedure in recent years, primarily due to a preference for RYGB and SG. AGB involves placing an adjustable silicone band around the upper part of the stomach to create a small pouch that restricts food intake, usually laparoscopically (O'Brien et al. 2006, Cohen et al. 2013). Due to the adjustable nature of the band, this procedure provides a customizable approach to weight loss based on patient progress. AGB may be an option for patients who prefer a reversible procedure or who are at higher risk for complications from more invasive surgeries, with its downside being the need for frequent follow-ups.

Weight loss with AGB tends to be more modest compared to RYGB and SG, with patients typically losing 40-50% of their excess body weight over a longer period (O'Brien et al. 2006). While AGB is associated with fewer nutritional deficiencies than RYGB due to the absence of malabsorption, it requires regular follow-up for band adjustments and has a higher rate of reoperation due to complications such as band slipping, erosion, or pouch dilation (Cohen et al. 2013).

2.4.4 Other Bariatric Procedures

In addition to RYGB, SG, and AGB, there are other bariatric procedures used for the treatment of obesity, though they are less commonly performed. These include:

- **Biliopancreatic Diversion with Duodenal Switch (BPD/DS)**: This procedure combines both restrictive and malabsorptive components and is effective for substantial weight loss,

particularly in patients with a very high BMI. However, it is associated with a higher risk of nutritional deficiencies and complications (Marceau et al. 2007).

- **Intragastric Balloon**: A non-surgical, temporary option involving the placement of a balloon in the stomach to reduce its volume. It is typically used for patients who need to lose weight before undergoing more definitive bariatric surgery (Genco et al. 2013).
- **Endoscopic Sleeve Gastroplasty (ESG)**: A newer, minimally invasive endoscopic procedure that reduces stomach volume without the need for surgical incisions. ESG is still being studied for its long-term efficacy and safety (Lopez-Nava et al. 2017).

2.5 Weighing Surgical and Pharmacological Options

In recent years, GLP-1 RAs have provided an alternative to surgical interventions for the treatment of obesity, with some options such as semglutide achieving 15-20% weight reductions. These medications work by enhancing satiety and reducing appetite, providing a less invasive option compared to bariatric surgery. However, the weight loss achieved with GLP-1 RAs tends to be less dramatic than that seen with surgical procedures such as RYGB and SG, which can result in excess weight loss of 50-80%.

One key advantage of pharmacological treatments is their non-invasive nature, which eliminates the risks associated with surgery, such as infections, leaks, or nutritional deficiencies. Pharmacological treatments can be particularly beneficial for patients who are not candidates for surgery or who prefer to avoid the risks and long-term commitments associated with surgical interventions. On the other hand bariatric surgery offers more durable and profound weight loss, particularly for patients with severe obesity and significant comorbidities.

The choice between bariatric surgery and pharmacological treatment depends on a variety of factors, including the patient's BMI, comorbid conditions, personal preferences, and ability to adhere to lifelong lifestyle modifications. For some patients, the combination of pharmacological therapy with lifestyle interventions may provide an effective alternative, while others may benefit more from the dramatic effects of surgery. Nevertheless, GLP-1 RAs are shaking the solid ground metabolic surgeries have stood on for decades.

3 GLP-1 RAs Market Dynamics and Future Developments

The obesity medication market has grown rapidly over the past few years, propelled by the entrance of GLP-1 RAs. As shown in Table 3.1, global obesity medication sales have experienced an approximate 220% increase between 2018 and 2022, dominated by GLP-1s which represented more than 90% of total sales in 2018. The US market has been the main driver of sales, as Europe approved a limited range of GLP-1 RAs for the treatment of obesity. The current chapter aims to provide clarity on market dynamics and competition, regulatory considerations, access and reimbursement in obesity.

3.1 Market Dynamics and Competition

Most of the anti-obesity medications explored in Chapter 2 have entered the market in the past decade, with orlistat receiving EMA approval in 1998 and FDA approval in 1999, preceded only by phentermine's EMA approval for weight management in 1956, and the FDA's in 1959. The latest treatment to enter both markets before the GLP-1 revolution were Qsymia, FDA-approved for obesity in 2012, and Mysimba, FDA-approved in 2014 and EMA-approved in 2015.

GLP-1s represent the newest treatment class and quickly taking center stage. In fact, GLP-1's dramatic overtaking of other medication classes for the treatment of obesity is staggering and reflected in Table 3.1, leading them to completely dwarf the rest by comparison. According to Evaluate Pharma (2023), in 2018 GLP-1s represented 73% of global sales in anti-obesity medications, while all other classes accounted for 27% of sales. In 2022, they reached 90%, with Saxenda and Wegovy accounting for 57% and 33% of global sales, respectively. For reference, Contrave and Qsymia accounted for 1% and 2% respectively.

	2018	**2019**	**2020**	**2021**	**2022**
GLP-1 RAs	613	852	859	1338	2419
Other	224	215	220	244	248
Total	**837**	**1067**	**1079**	**1582**	**2667**

Table 3.1: Global Obesity Sales ($M)
Source: Global Data

Saxenda, initially marketed as Victoza for T2D, was first launched in the US in 2014 as a subcutaneous GLP-1 monotherapy, achieving $627 million in sales by 2022. In 2015, it was introduced in the EU, reaching $511 million in sales by 2022. Saxenda's success has contributed to market development since its launch, paving the way for Wegovy and other subsequent anti-obesity medications.

Wegovy entered the US market in 2021 and the EU market in 2022, offering enhanced efficacy over Saxenda and a more convenient dosing schedule for a subcutaneous therapy. Although Wegovy benefited from a favorable environment shaped by Saxenda's success, its entry also marked the beginning of an increasingly competitive market. High demand for these medications eventually led to significant supply chain challenges and saturation issues (J.P. Morgan 2023A). Wegovy is also a GLP-1 monotherapy, though future developments are exploring GLP-1 combinations with other agents, potentially from the same or different therapeutic classes.

The anti-obesity medication market is espected to keep growing at a considerable pace, with forecasts evaluating their market to reach approximately $70bn by 2032 (J.P. Morgan 2023B, Morgan Stanley 2023). This growth will likely be driven by improved access and reimbursement across markets, especially if obesity continues to gain recognition as a chronic disease by healthcare institutions. Additionally, the global incidence of obesity and related comorbidities is expected to increase, further growing the eligible population for these treatments. Advancements such as the introduction of long-acting therapies like Cagrisema and tirzepatide, along with new products featuring oral routes of administration instead of the predominantly subcutaneous options available today, are expected to address key deterrents from the patient perspective (Global Data 2023).

Given the efficacy and safety profiles of GLP-1s, as discussed in the previous chapter, other treatment classes such as lipase inhibitors and anorexigenics are expected to continue losing market share, although they will still serve as second- and third-line treatments. The introduction and performance of GLP-1s are bound to fundamentally reshape the previous treatment

paradigm presented in Figure 2.1. GLP-1s, either alone or in combination, will likely become the first-line treatment alongside lifestyle modifications. Meanwhile, other medication classes will serve as second-line options for patients who are contraindicated for GLP-1s or cannot tolerate them. Surgical interventions, such as bariatric surgery, and medical devices, like gastric balloons, will remain the final line of defense in combating obesity.

The narrative for the T2D market is quite similar to the one just outlined for obesity. The T2D market is expected to continue expanding, driven by increases in both prevalence and diagnosis, as well as an increased use of GLP-1s. Among the GLP-1s, Ozempic, Rybelsus and Mounjaro represent the leading therapies. However, the diabetes market is expected to grow at a slower rate than the obesity market (Global Data 2022, 2023), despite the overlap bewteen the two markets.

3.1.1 GLP-1 Pipeline Analysis

The GLP-1 pipeline shows a dynamic and evolving landscape, characterized by numerous innovations aimed at improving treatment efficacy and patient outcomes. Drawing from the Global Data database, this subsection will focus on GLP-1 candidates that are actively in trial, excluding those that are already marketed without ongoing trials, as well as those that have been discontinued, withdrawn, or are otherwise inactive. Additionally, research conducted solely by universities and institutions is not considered, emphasizing industry-driven innovation. The geography has been restricted to EU and US countries, although the overwhelming majority of assets is being tested for international approval.

Currently, Eli Lilly and Novo Nordisk dominate the GLP-1 market, leveraging their early investments and robust portfolios. Novo Nordisk's key products include Ozempic and Rybelsus for diabetes, as well as Wegovy for obesity, all of which are GLP-1-based therapies. In addition, Novo Nordisk offers Victoza, another GLP-1 therapy for diabetes, and Saxenda, which targets obesity. Eli Lilly, on the other hand, markets Trulicity and Mounjaro (a dual GIP/GLP-1 receptor agonist) for diabetes, as well as Jardiance, a non-GLP-1 SGLT2 inhibitor for diabetes, which contributes to their extensive diabetes care portfolio. However, significant shifts may be on the horizon as innovations in the pipeline and impending loss of patent exclusivity for existing drugs open doors for new competitors. Emerging therapies, including combination treatments and novel GLP-1 formulations, have the potential to enhance efficacy, reduce side

effects, and improve patient adherence. Both bigger and smaller pharmaceutical companies are seeking to capitalize on these opportunities, so that the competitive landscape is expected to become increasingly diversified, challenging the incumbents and altering the current market dynamics.

Currently, the GLP-1 pipeline includes 100+ unique assets in various stages of development across the relevant geographies. Among them, approximately 10% are combinations of GLP-1s and other drugs, while the rest are GLP-1 monotherapies. Therapy areas are incredibly varied, spacing the expected metabolic disorders such as obesity and diabetes, or gastrointestinal conditions such as MASH and liver cirrhosis, liver fibrosis, both primary biliary and primary sclerosing cholangitis, and respiratory conditions commonly associated with obesity such as obstructive sleep apnea. New areas of interest for the class are central nervous system conditions like Alzheimer's disease, Lewy Body dementia, Parkinson's disease, neuropathies, intracranial hypertension, multiple sclerosis, smoking cessation and binge eating disorder. Furthermore, genetic disorders and musculoskeletal disorders such as muscular dystrophies, sarcopenia and more.

Eli Lilly's Zepbound (GLP-1/GIP targeting) appears more promising than Wegovy, achieving a 21% body weight loss in the SURMOUNT trials, as opposed to the 16% Wegovy achieved in its pivotal Phase III trial (Garner and Pagliarulo 2024). Although Zepbound has yet to establish its ability to prevent cardiovascular complications as Wegovy has, the ongoing SURPASS-CVOT trial aims to evaluate this crucial aspect. On the other hand, Novo Nordisk is investing in Cagrisema, a dual acting experimental drug whose Pahse III REDEFINE1 trial results are expected to be published at the end of 2024 (clinicaltrials.gov 2024).

A comprehensive overview of the pipeline is provided in Figure 3.1 for metabolic disorders and Figure 3.2 for other therapeutic areas. Pipeline data comes from the Global Data pharmaceutical database, which offers comprehensive insights into the entire drug development lifecycle, from discovery and clinical development to regulatory submission and commercialization (excluding prices). Notably, the pipeline exhibits a shift away from subcutaneous formulations, especially in established GLP-1 therapeutic areas like obsity and T2D, towards oral formulations which now constitute approximately 25% of the pipeline. Both Novo and Lilly are trialling oral formulations of their marketed products, and many aspiring entrants are betting on patients preferring a pill over a subcutaneous injection. A notable example in this regard is

Roche, which acquired Carmot Therapeutics in 2023 to access its three obesity drugs, including the oral CT-996 GLP-1 currently in Phase I (Fidler 2024). Other players such as Pfizer and Structure Therapeutics have oral assets in Phase II. The most prominent manufacturers in the GLP-1 space remain Novo Nordisk and Eli Lilly, which control 22.6% and 10.7% of the pipeline, respectively.

Although the main focus remains on metabolic disorders such as T2D and obesity, a significant portion of the pipeline now focuses on ther disease areas. Among them, neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, and liver conditions such as metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated steatotic liver disease (MASLD) are attracting considerable resources.

GLP-1's growth-factor and neuroprotective properties have motivated research into GLP-1 RAs as a potential treatment for Parkinson's and Alzheimer's. These neurodegenerative conditions are characterized by brain impairment linked to mitochondrial dysfunction, neuroinflammation, vascular changes, and neurotransmitter alterations. The GLP-1 hormone has been shown to influence various neuronal functions, including thermogenesis, neurodegeneration, neurogenesis, and blood pressure regulation. Additionally, studies point to GLP-1 receptors and glucose-dependendent insulinotropic polypeptide (GIP) receptors' genetic variability as a factor influencing the occurrende of Alzheimer's and Parkinson's (Grieco et al. 2019, Vogrinc et al. 2024, Hölscher et al. 2022). At the moment, 9.7% of the pipeline consists of central nervous system disease assets, mostly focused on these two diseases.

In the gastrointestinal disease area we can find 21.5% of all pipeline assets, all focused on either MASH or MASLD. MASLD is the precursor stage to more severe MASH, with both liver conditions being associated with insulin resistance, chronic inflammation, and lipid accumulation, all of which contribute to disease progression and may benefit from the effects of GLP-1 RAs. GLP-1 RAs have demonstrated the ability to improve insulin sensitivity, reduce hepatic fat content, and attenuate inflammation, addressing key aspects of MASH and MASLD pathophysiology. Additionally, evidence suggests that GLP-1 receptor activation can enhance mitochondrial function and reduce oxidative stress in the liver, further supporting its therapeutic potential (Yabut et al. 2023, Nevola et al. 2023, Abushamat et al. 2024). MASH and MASLD share a strong link with T2D and obesity, and are often considered hepatic manifestations of those metabolic disorders. Insulin resistance, a central feature of T2D, leads to increased fat

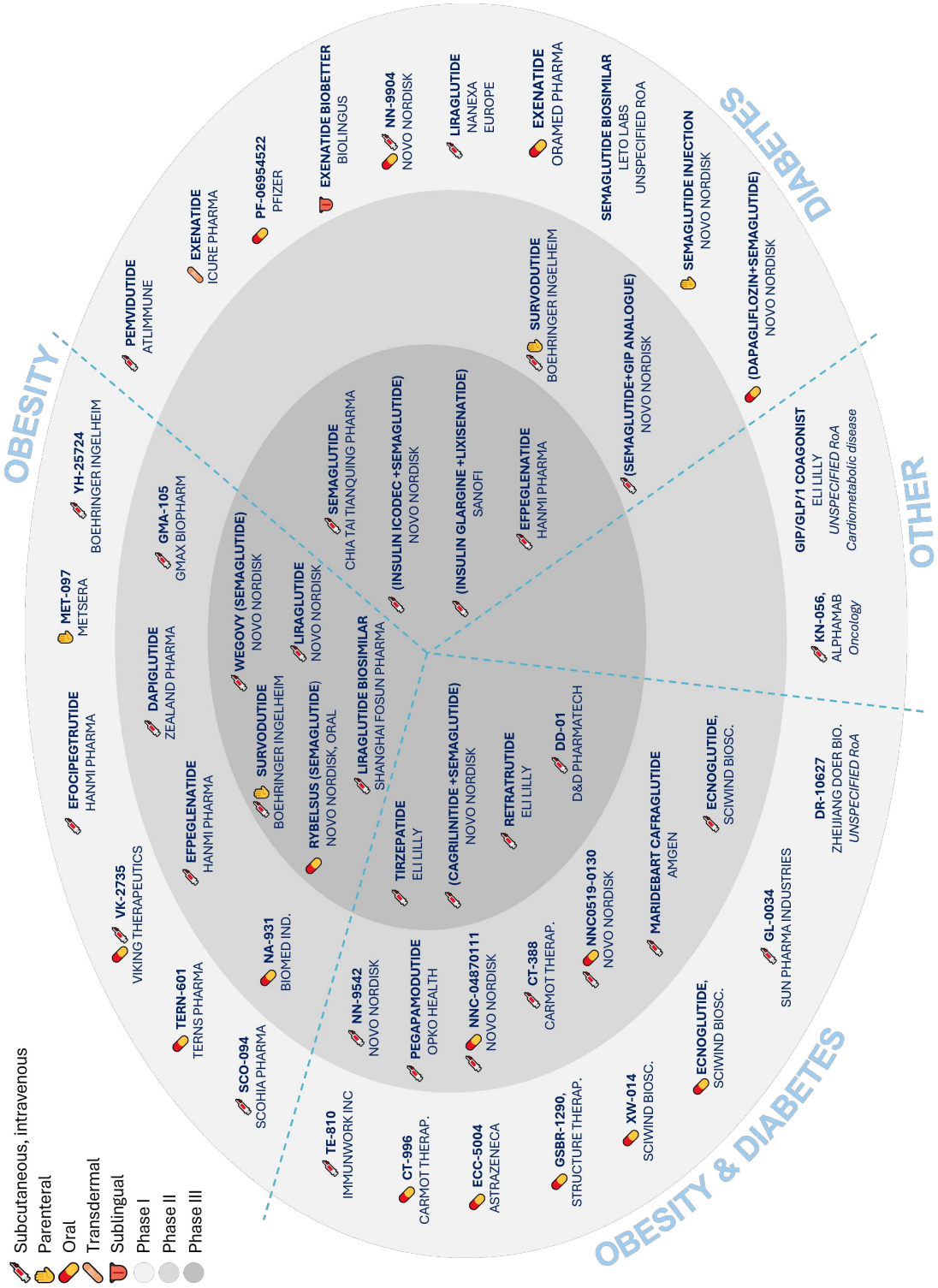


Figure 3.1: GLP-1 pipeline for metabolic disorders
Source: Global Data, 2024.

Excluding: marketed, withdrawn, inactive, preclinical, discontinued, discovery, universities and institutions, non-EU. Abbreviations: RoA=route of administration

deposition in the liver, promoting steatosis and inflammation, which drive the progression from simple fatty liver disease to MASLD and, eventually, MASH. Obesity further exacerbates this process due to the excess adipose tissue releasing pro-inflammatory cytokines and free fatty acids that contribute to liver injury and fibrosis (Bray 2004, Yabut et al. 2023, Cao 2014).

The high and growing prevalence of T2D and obesity is driving a growing population for MASH and MASLD via their frequent comorbidity. The unmet need for these liver diseases is substantial due to the conditions' progressive nature and the limited availability of effective treatments. Current management strategies for MASH and MASLD rely on lifestyle interventions, and as such are often inadequate as patients sruggle to achieve and maintain the necessary changes. However, liver diseases and neurodegenerative conditions present alternative avenues for obtaining reimbursement for GLP-1 receptor agonists in countries like Germany, where regulatory barriers limit reimbursement for obesity treatments. Pharmaceutical companies investing in these diseases is not the pursuit of better treatments for underserved conditions, but also a way to seize the opportunity to reach patients who could benefit from GLP-1 receptor agonists yet face access barriers due to regulatory restrictions. By focusing on comorbidities such as liver diseases, cardiovascular disorders and respiratory conditions that frequently develop as complications of obesity, these companies are strategically expanding their reach to populations indirectly affected by obesity. This approach allows to navigate reimbursement limitations by targeting conditional with overlapping metabolic risk factors and, as such, broadening the therapeutic impact of GLP-1 therapies.

3.2 Regulatory, Access and Reimbursement

The regulatory lanscape for GLP-1s is complex and reflects the growing recognition of their therapeutic potential, starting from diabetes and obesity. This section aims to provide an overview of the trial requirements for EMA and FDA approval, the current regulatory status of GLP-1s, ongoing development and future challenges.

3.2.1 Benchmark Requirements for Phase III Trials

The FDA's "Guidance for Industry: Developing Products for Weight Management: Revision 1" (FDA 2007) outlines the approval requirements for anti-obesity medications. The minimum

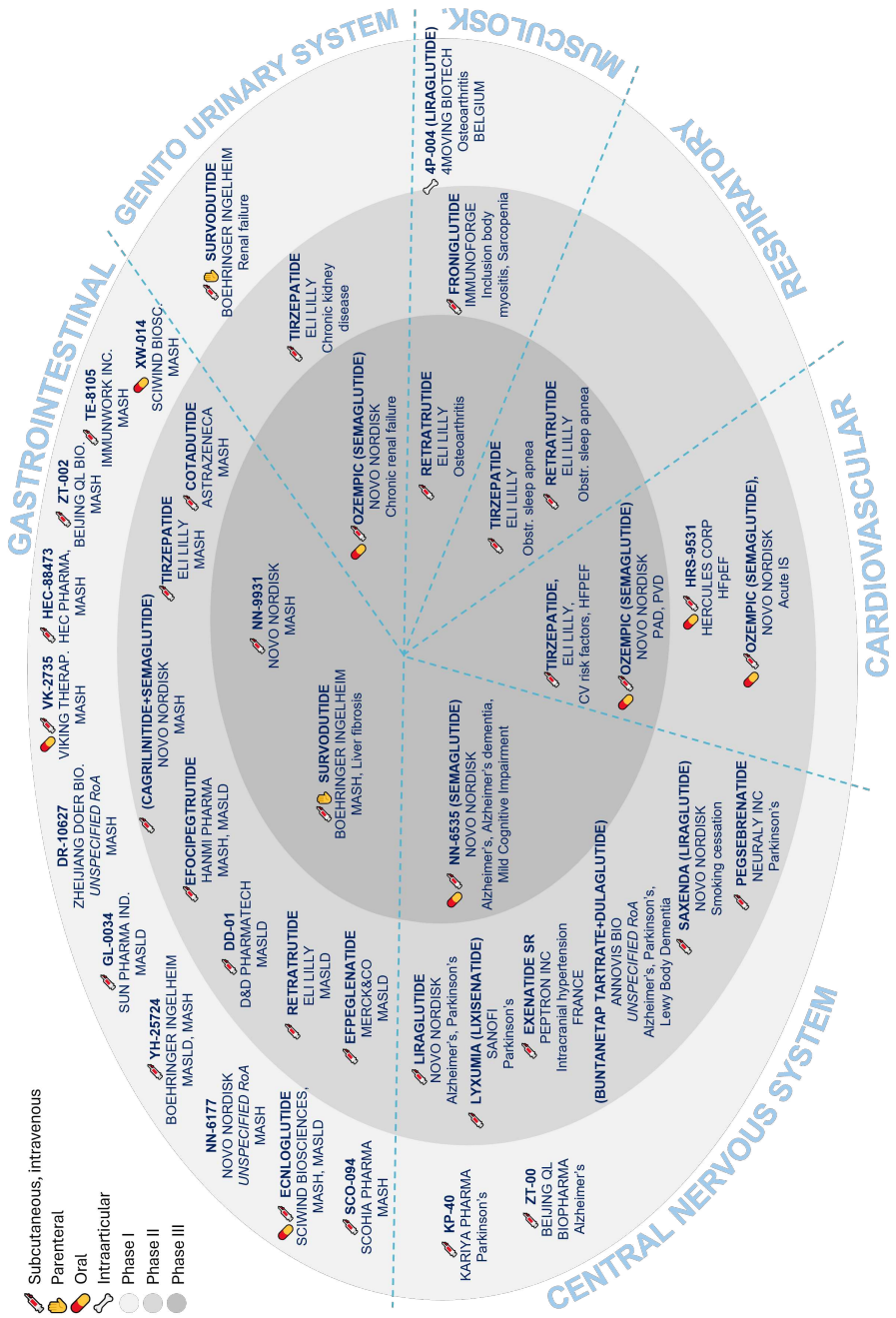


Figure 3.2: GLP-1 pipeline for other disease areas
Source: Global Data, 2024.

Excluding: marketed, withdrawn, inactive, preclinical, discontinued, discovery, universities and institutions, non-EU. Abbreviations: PVD=peripheral artery disease, PVD=peripheral vascular disease, IS=ischemic stroke, CV=cardiovascular, HFpEF=heart failure with preserved ejection fraction, RoA=route of administration, MASH=metabolic dysfunction-associated steatohepatitis, MASLD=metabolic dysfunction-associated steatotic liver disease

efficacy benchmarks stipulate that, compared to placebo, the treatment must achieve at least a 5% reduction in excess weight after one year, and at least 35% of the treatment group must experience weight loss greater than 5%.

The EMA's "Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management" (EMA 2016) specifies similar efficacy criteria, requiring a placebo-corrected weight loss of at least 5% after one year, with at least 10% of patients in the treated group maintaining that weight loss at the end of the 12-month period. In addition to efficacy requirements, both agencies demand that trial design, size, and duration adhere to a precise set of standards.

All of these benchmarks have been successfully met by various GLP-1 therapies.

3.2.2 Access and Reimbursement of GLP-1s in European Markets

This section is informed by internally developed reports and sensitive project-related deliverables sourced from Charles River Associates. Due to the sensitive and proprietary nature of these materials, they cannot be publicly shared; however, they can be cross-referenced by internal staff at the Munich office upon request.

The coverage and reimbursement for anti-obesity medications in the United States vary significantly depending on the Pharmacy Benefit Manager (PBM) channel. Commercial insurance channels currently provide the majority of anti-obesity medications coverage, whereas Medicare prohibits coverage of these medications under Part D. Managed Medicaid and Health Exchange plans also offer limited coverage, with state Medicaid providing preferred access, albeit on a state-specific basis.

To obtain coverage for anti-obesity medications, prior authorization (PA) requirements are common and often go beyond the conditions listed on the product label, posing an additional barrier for patients seeking treatment. As a result, access is often restricted to those who meet highly stringent criteria. The financial burden is further compounded by the high cost of newer anti-obesity medications, such as Saxenda and Wegovy, whose monthly list prices average around $1,350 USD, making them largely unaffordable for patients without substantial insurance coverage.

Outside the United States, the reimbursement landscape is quite different. While antidiabetic drugs for T2D are widely reimbursed, obesity medications face significant restrictions, often due to concerns about their long-term impact and lack of recognition of obesity as a dis-

ease. Health Technology Assessment (HTA) agencies acknowledge the unmet need for effective obesity treatment and the clinical superiority of newer therapies but continue to emphasize a lack of robust evidence for long-term cardiovascular outcomes, comorbidities, and mortality benefits. This has hindered widespread coverage of anti-obesity medications in many countries.The monthly cost for Saxenda and Wegovy in Europe ranges from €177 (Saxenda Italian price, not reimbursed) to €249 (Wegovy German price, not reimbursed), which, while lower compared to the US, remains a barrier for many patients. The reimbursement decisions for these drugs vary across European countries. Some countries have adopted positive coverage policies with restrictions, requiring patients to meet specific criteria before coverage is approved. Other regions, like Germany and France, have maintained more restrictive policies, while countries like the United Kingdom and the Scandinavian nations show a mixed but evolving approach towards reimbursement.

Germany, one of the largest pharmaceutical markets in Europe, does not recognize obesity as a disease but rather classifies it as a lifestyle condition. Consequently, obesity medications are treated as lifestyle treatments and are excluded from reimbursement. The likelihood of future reimbursement remains limited unless these drugs expand their EMA-approved indications beyond weight loss, for instance by including cardiovascular event prevention, or until there is a regulatory shift regarding lifestyle treatments. On the other hand, T2D GLP-1 medications such as Victoza (€104 monthly price) and Ozempic (€117 monthly price) are reimbursed according to their label, although the Ozempic HTA outcome yielded no added benefit.

In France, obesity is recognized as a chronic disease, however the reimbursement of obesity medications remains limited and highly restricted. The ongoing reimbursement negotiations for Wegovy offer a promising outlook for the potential expansion of coverage in the future. T2D GLP-1s such as Victoza (€76 monthly price) and Ozempic (€143 monthly price) are both reimbursed under ASMR IV (Amélioration du Service Médical Rendu IV, indicating a minor incremental benefit compared to previously approved alternatives).

In Italy, although obesity was officially recognized as a chronic disease in 2019, bariatric surgery remains the only reimbursed treatment option. Expanding reimbursement to include pharmacological treatments will depend on AIFA's willingness to reconsider, which may be influenced by emphasizing the observed improvements in patient outcomes, including disease remission and a reduction in complications. For T2D, Italy provides reimbursement for Victoza

(€90 monthly price) as a Class A medication, whereas Ozempic (€246 monthly price) is classified under Class C(nn), meaning it is not currently reimbursed but may be reconsidered in the future.

In Spain, obesity is recognized as a chronic disease by the Ministry of Health. Reimbursement of obesity treaments varies by regions, however anti-obesity pharmacological options are excluded. In T2D, Spain reimburses Victoza (€75 monthly price) for patients with the disease and a BMI$\geq$30, and Ozempic (€178 monthly price) is covered as a dual or triple therapy in patients with T2D and BMI$\geq$30.

Moving forward, analysts expect European prices for anti-obesity drugs to remain stable between €150-250 per month, with potential for a slight decrease. Upwards prices pressure comes from the entrance of innovative medications with improved efficacy and proven benefits to comorbid conditions and cardiovascular risk factors,, growing patitent populations, as well drugs aiming at more targeted subpopulations that could demand higher prices. Downward prices pressure comes from the healthcare systems pushing for lower prices to contain reimbursement costs, as well as strong incoming competition from new products. Loss of exclusivity of certain molecules (e.g. Wegovy in 2031) will allow the entrance of generics on the market, stimulating price erosion and competition, as well as pushing for more innovation.

In summary, the regulatory, access, and reimbursement landscape for GLP-1 therapies is marked by complexity and variability across different markets. While the regulatory benchmarks set by the FDA and EMA have been successfully met by various GLP-1 therapies, the access and reimbursement scenario remains challenging. Countries like the United States, France, Italy, and Spain present diverse reimbursement policies influenced by the local recognition of obesity as a disease, cost considerations, and regulatory dynamics. Moving forward, finding the balance between innovation, pricing pressures, and evolving regulatory landscapes will determine the extent to which GLP-1 therapies can reach broader patient populations. Continued advocacy for recognizing obesity as a chronic disease, along with new evidence on cardiovascular and long-term health benefits, will be crucial in shaping a more inclusive reimbursement landscape. Contemporaneously, companies are focusing a sizeable portion of their investment in disease areas outside of metabolic conditions like T2D and obesity, where GLP-1s have already proven their efficacy.

CHAPTER 3. GLP-1 RAS MARKET DYNAMICS AND FUTURE DEVELOPMENTS

4 Discussion and Conclusion

The objective of this thesis was to explore the evolving obesity treatment landscape, which has undergone significant innovation in recent years, largely driven by the introduction of GLP-1 receptor agonists, and pinpoint future shifts caused by the entrance of these new medications. Chapter 1 provided a comprehensive overview of obesity, and highlighted its link to comorbid conditions as well as its burden on an individual and system level. Chapter 2 provided an in-depth analysis of the available treatment options, starting from the least effective lifestyle interventions and finishing with an analysis of commonly employed surgical options. More importantly, it introduced and explored the evidence surrounding old and new pharmacological treatments approved for obesity management, showing GLP-1 RAs superiority to preceding drugs. Chapter 3 discussed the market dynamics surrounding the entry of GLP-1s, with an emphasis on regulatory developments, current pipeline activity, and the broader implications for future obesity management.

GLP-1s have proved their superior safety and efficacy profile relative to older pharmacological alternatives, achieving weight loss in excess of its non-GLP-1 competitors. While surgical interventions may still be more effective in the most severe cases, GLP-1s offer a non-invasive, safer, and efficacious alternative for managing obesity across a broad range of patients who have not responded to other treatments. Furthermore, GLP-1s have the versatility to enter at various stages of the tratment paradigm, providing options across age groups and genders.

Despite these advantages, ene of the greatest challenges to overcome will be achieving reimbursement in countries that do not yet recognize obesity treatments as susceptible to reimbursement. Nevertheless, pharmaceutical companies are focusing considerable effort and resources on diversifying their portfolios across assets and disease areas, as manifested in a particularly active drug pipeline. In doing so, they are aiming to expand the patient population receiving reimbursable treatments by targeting obesity's comorbid conditions such as liver diseases,

metabolic disorders, cardiovascular and respiratory conditions. In addition, GLP-1's mechanism of action is motivating considerable investment in musculoskeletal and central nervous system diseases. Although both small and big pharmaceutical companies are participating in the race, current and future key players are likely to remain unchanged and consist of companies like Novo Nordisk and Eli Lilly, who currently possess the more promising marketed assets.

In conclusion, all points to GLP-1s continuing to displace previously marketed treatment options across a variety of obesity comorbid diseases, as well as entering new and underserved indications. The impressive growth in market share and revenue for obesity and T2D is likely to continue, while GLP-1s will attempt to replicate this astounding success across areas such as metabolic associated liver diseases. The expanding indications, active pipeline, and ongoing investment in diverse therapeutic areas indicate that GLP-1s are poised to redefine the treatment landscape not just for obesity and T2D, but potentially for a range of chronic conditions.

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