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CHAPTER 7

GLP-1 ANALOGUES: THE NEW FRONTIER IN OBESITY TREATMENT

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ABSTRACT

GLP-1 analogues, a pharmacological class widely used in the management of type II diabetes, have gained prominence for their role in weight loss. Their frequent and often inappropriate use for weight reduction beyond their original indication underscores the need for a deeper understanding of their effects and proper guidance on their use. These drugs act through multiple mechanisms, promoting weight loss by stimulating satiety, increasing insulin sensitivity, lowering glucagon levels, and delaying gastric emptying. Liraglutide and Semaglutide, the main representatives of this class, have demonstrated efficacy in weight reduction, albeit with differences in their action profiles and outcomes. However, therapeutic success depends on a multidisciplinary approach, where the use of GLP-1 analogues is only one component of treatment. The adoption of complementary strategies, such as lifestyle and dietary changes, is essential to ensure that results are sustainable and meaningful in the long term. The active participation of pharmacists in this context is crucial, both in providing appropriate guidance and in supervising the correct use of these medications, thereby ensuring the safety and efficacy of treatment. Thus, GLP-1 analogues present themselves as a promising alternative in the management of overweight, when used consciously and within a broader therapeutic framework.

Keywords: Obesity; Diabetes; Hypocaloric; Liraglutide; Semaglutide.

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INTRODUCTION

Obesity and overweight constitute a public health issue that places a significant burden on Brazil's Unified Health System (SUS). Recognized as a chronic, progressive, and recurrent disease, obesity is considered a global epidemic by the World Health Organization (WHO). According to Brazil's Ministry of Health, over one (1) billion adults worldwide are overweight. In addition to being a multifactorial risk condition, obesity involves numerous variables that contribute to the development of various other pathologies, notably type II diabetes, which is the primary therapeutic target for GLP-1 analogues.

GLP-1 analogue drugs enhance insulin production in response to glucose, delay gastric emptying—thereby promoting satiety—and inhibit hunger signaling and the action of the hormone glucagon. Their effects on weight loss have been well received, particularly among individuals pursuing aesthetic goals. However, there remains limited information regarding their potential side effects, contraindications, and, most importantly, their rational use in dietary re-education. The increasingly frequent and inappropriate use of GLP-1 analogues for weight loss, diverging from their original purpose in managing type II diabetes, highlights the need for a more comprehensive understanding of their therapeutic role. Investigating these medications as adjuvants in weight loss treatment is crucial—not only to provide more effective guidance to patients but also to foster a paradigm shift in addressing the issue, emphasizing the importance of physical activity and healthy eating habits.

GLP-1, a hormone produced in the small intestine, plays a fundamental role in regulating blood glucose and satiety. Studies have shown that GLP-1 analogues such as Liraglutide and Semaglutide are also effective in reducing body weight in overweight and obese patients. These medications act by delaying gastric emptying, which promotes a sensation of fullness, and by suppressing hunger. Therefore, the research problem defined in this study is to understand how these drugs influence the weight loss process. This understanding is essential to explore their therapeutic potential in this context and to develop more effective and personalized strategies tailored to individual treatment plans.

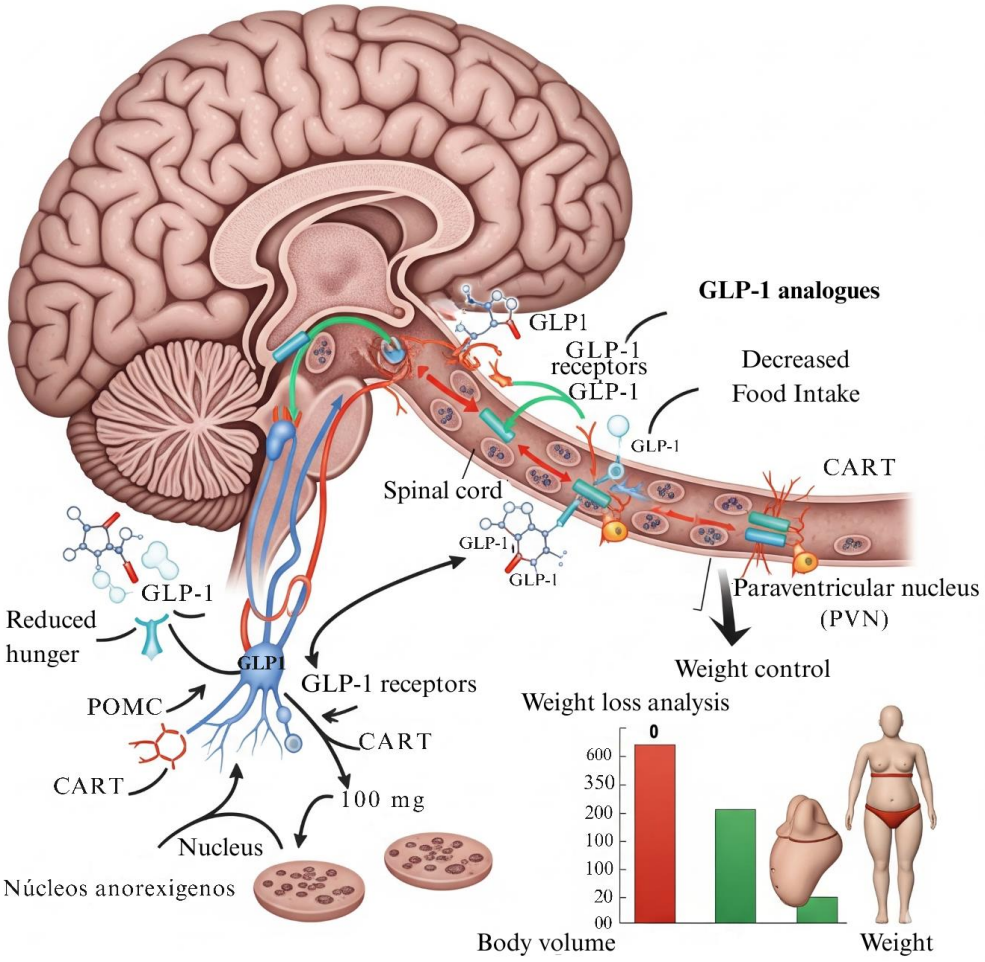
PHARMACOLOGY AND THE IMPACTS OF GLP-1 ANALOGUES

Incretin hormones have recently become the focus of scientific investigation due to their crucial role in appetite regulation. It is now known that these hormones are produced and secreted by the gastrointestinal tract in response to the presence of nutrients in the intestinal wall. GLP-1, an essential intestinal peptide belonging to the class of anorexigenic hormones, is the principal incretin. Its release is influenced by nutrients in the intestine, particularly carbohydrates (Barbosa et al., 2022). GLP-1 enhances insulin secretion in a glucose-dependent manner, reduces glucagon secretion, delays gastric emptying, and suppresses appetite by acting as an agonist at its receptors. These mechanisms contribute to weight

loss in patients (Heinla et al., 2023; Tambascia et al., 2023).Individuals with overweight are at increased risk of developing a range of serious comorbidities, including cardiovascular diseases, type II diabetes, musculoskeletal disorders, and psychological conditions (Sant'ana, 2023). In this context, GLP-1 analogues emerge as promising treatment options for adults with excess weight and comorbidities, promoting weight loss, regulating glucagon release, slowing gastric emptying, and improving insulin sensitivity (Rodrigues et al., 2018). Although originally developed for the treatment of type 2 diabetes, these medications are often prescribed "off-label" for weight loss and may be used long-term or continuously (De Castro et al., 2022).

GLP-1 performs several critical functions, including stimulating proinsulin production, regulating the secretion of insulin and somatostatin, modulating α-cells by inhibiting glucagon release, controlling appetite by enhancing satiety, promoting weight loss, and suppressing hunger-inducing signals in the hypothalamus. Additionally, it reduces intestinal motility and delays gastric emptying, while also inhibiting gastric acid secretion postprandially, thereby enhancing satiety (Andreasen et al., 2021).

Figure 1 – Influence on the hypothalamus: regulation of anorexigenic neurotransmitter release



Source: Adapted. Authors, 2025

Weight loss and its maintenance are complex challenges; the body tends to resist weight reduction by increasing hunger and decreasing satiety when a caloric deficit is detected, often leading to weight regain (De Castro et al., 2022). The rebound effect associated with these behavioral patterns—where individuals regain lost weight and even gain additional weight after discontinuing medication—underscores the need for integrated and sustainable approaches to address this persistent and challenging condition (Barbosa et al., 2022).

The glucose-dependent insulinotropic polypeptide (GIP), produced and secreted by K cells in the duodenum and jejunum, stimulates insulin release from the pancreas following glucose ingestion. Conversely, glucagon-like peptide-1 (GLP-1), secreted by L cells in the intestine (see Figure 1), activates insulin biosynthesis and secretion by β-cells and inhibits receptor release. Its metabolism by the serine protease enzyme dipeptidyl peptidase-4 (DPP4) was pivotal in the development of GLP-1 receptor agonists and DPP4 inhibitors (DPP4i), leading to the emergence of incretin-mimetic drugs for the treatment of type 2 diabetes mellitus (Andreasen et al., 2021).

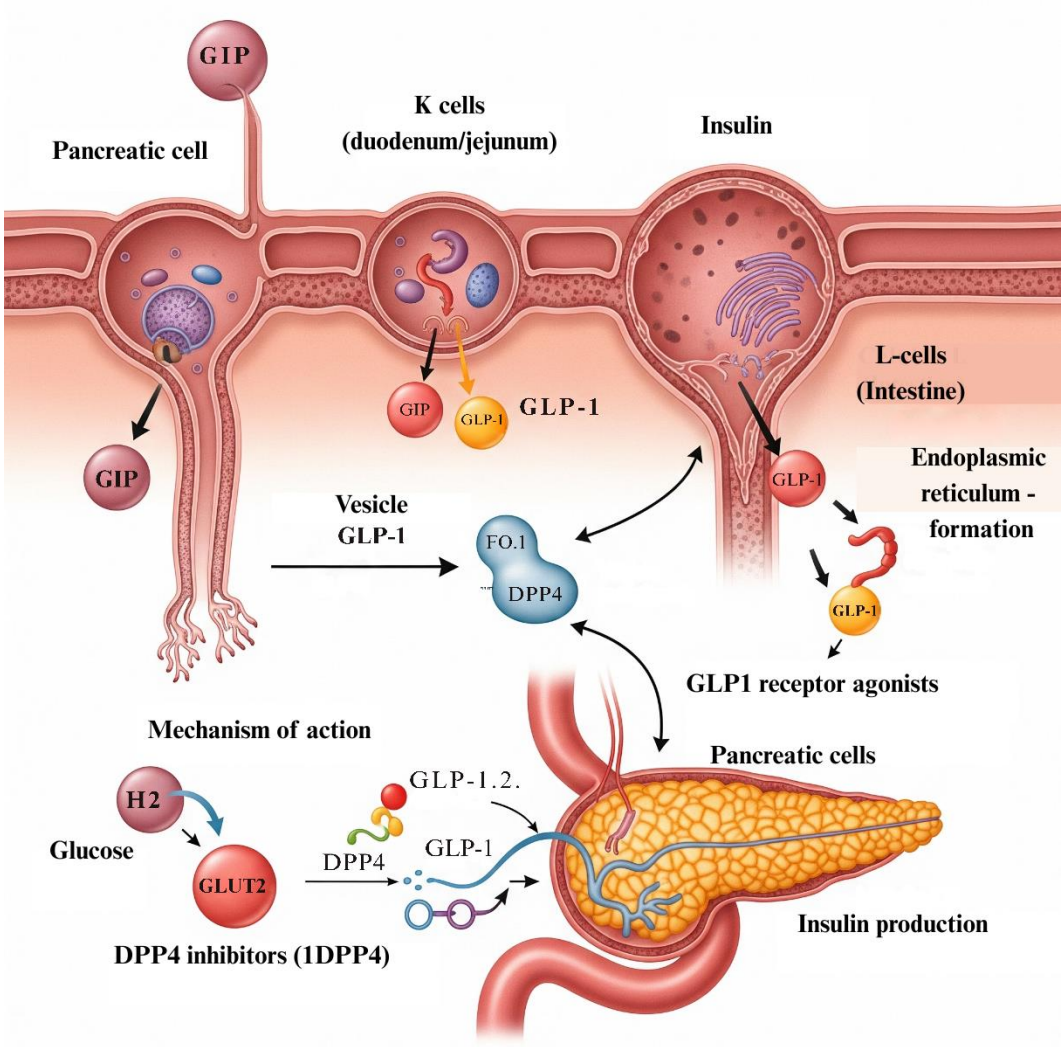
Table 1 - Physiological Actions of Glucagon-Like Peptide-1 (GLP-1).

Aspect	Description and Function
Action in the Stomach	- Slows gastric emptying. - Provides a prolonged sensation of satiety. - Helps control appetite and reduce food intake. - Contributes to weight management and obesity control.
Interaction with the Pancreas	- Stimulates insulin secretion, essential for blood glucose control. - Inhibits glucagon production, which raises blood glucose levels. - Maintains glycemic homeostasis, vital for metabolic health.
Influence on the Hypothalamus	- Activates the release of anorexigenic neurotransmitters. - Reduces hunger, contributing to decreased food intake. - Supports the use of GLP-1 analogues in weight-related disorders.
Summary of Functions	GLP-1 promotes satiety, stimulates insulin release, and inhibits glucagon, making it an effective option for treating obesity and type II diabetes by helping regulate appetite and blood glucose levels.

Source: Brunton et al., 2021.

Other significant effects of GLP-1 include improvements in fasting and postprandial lipid profiles (reducing triglycerides and free fatty acids), its lipolytic capacity, reduced hepatic glucose output, and increased hepatic insulin sensitivity. These effects stimulate glycogenesis and facilitate glucose uptake in muscle and adipose tissues (Del-Vechio et al., 2016).

Figure 2 – The DPP4 Enzyme and Drug Development



Source: Adapted. Authors, 2025

Over time, treatments have been developed focusing on appetite regulation through combined approaches, with the primary goal of promoting weight loss. The use of incretins—particularly GLP-1—as a therapeutic target was first established for the treatment of type 2 diabetes in the early 20th century, when Bayliss and Starling demonstrated that GLP-1 accounts for up to 70% of insulin secretion in response to nutrient intake. This discovery led to the development of drugs such as liraglutide (Saxenda®). Later, the weight loss benefits of GLP-1 analogues were also demonstrated (Pessoa, 2023).

Due to its effect on slowing gastric emptying, concurrent use with other orally administered medications may interfere with absorption, although this is generally not clinically significant. While studies suggesting contraindications for GLP-1 analogues in pregnant women are inconclusive, they are sufficient to raise concerns about potential high risk. Animal studies have shown genotoxicity, while the risk during human pregnancy remains unknown (De Sá et al., 2023).

According to Bratti et al. (2023), the timing of drug administration is a crucial factor in evaluating the weight-reducing effects of semaglutide. They observed that weekly dosing was well tolerated for up to one year, resulting in clinically significant weight loss compared to placebo across all doses. This highlights the importance of assessing dose tolerability to achieve the desired weight reduction. Therefore, individualized patient evaluation and regular monitoring are essential to detect potential adverse effects or lack of efficacy with the initially prescribed dose (Pires et al., 2023).

In the primary treatment phase, Wadden et al. (2021) observed improvements in cardiovascular risk factors in patients using semaglutide, including reductions in systolic and diastolic blood pressure, C-reactive protein (CRP), and lipid levels. However, after discontinuation of treatment, average systolic and diastolic pressures increased in both treatment groups, returning to baseline levels by week 120. Regarding CRP and lipid levels, individuals who received semaglutide showed increases after stopping the medication, although levels remained below those of the placebo group. It is important to emphasize that exclusive reliance on this medication, without effective lifestyle changes, may hinder the maintenance of therapeutic outcomes and compromise accurate assessment of semaglutide's short-, medium-, and long-term effects. Therefore, multidisciplinary follow-up is essential to ensure that the positive effects outweigh the potential risks of pharmacological therapies aimed at weight loss in non-diabetic individuals.

LIRAGLUTIDE AND SEMAGLUTIDE, GLP-1 ANALOGUES – PRACTICAL EFFECTS IN PROMOTING WEIGHT LOSS

There is a growing demand for medications to treat overweight and obesity, although caution must be exercised when considering their use, taking into account the side effects, indications, and specific contraindications of each drug. Increasing doses beyond the recommended levels merely intensifies adverse effects without providing additional benefits to the patient. It is crucial to understand that no drug is entirely effective or completely safe (Barbosa et al., 2022).

Among the available GLP-1 analogue medications, Liraglutide (commercially known as Saxenda® and Victoza®) is widely recognized and used, having been approved for use in Brazil. Liraglutide promotes satiety and reduces food intake in two ways: by increasing leptin levels after meals and by delaying gastric emptying. Initially developed to treat type 2 diabetes, Liraglutide is a synthetic substance with 97% similarity to GLP-1. Studies indicate that daily doses of 3.0 mg of Liraglutide reduce hunger, decrease food intake, and delay gastric emptying in obese patients without diabetes. However, the safety and efficacy of this medication in patients with severe cardiac, renal, or hepatic insufficiency are not well understood, making its use inappropriate for these individuals (ANVISA, 2020)..

In a study conducted to evaluate the safety and efficacy of Liraglutide as a pharmacological adjunct combined with physical exercise and diet in the treatment of obese adults with type 2 diabetes, Liraglutide was examined in doses ranging from 1.8 to 3.0 mg over 56 weeks. Participants were randomly divided into three groups: one receiving 1.8 mg of Liraglutide once daily, another receiving 3.0 mg once daily, and a placebo group. The average weight loss was 4.7% in the 1.8 mg group, 6.0% in the 3.0 mg group, and 2.0% in the placebo group. It was observed that the groups using Liraglutide experienced weight loss ranging from 5% to over 10% of their initial body weight, along with improvements in glycemic control and blood pressure. The most common adverse effects were transient and included nausea and gastrointestinal disturbances (Davies et al., 2015).

The emergence of Semaglutide, driven by the goal of developing a once-weekly medication for individuals with type 2 diabetes mellitus, resulted in more significant weight loss compared to Liraglutide and other GLP-1 receptor agonists. Furthermore, a safety profile was observed that allowed for expanded therapeutic use in overweight individuals, regardless of diabetic status (Knudsen, 2019).

Semaglutide, marketed as Ozempic®, is indicated for treatment in adults with type 2 diabetes, in conjunction with diet and exercise. As a member of the incretin mimetic class and a synthetic GLP-1 analogue, Semaglutide directly impacts body weight and is frequently used in overweight patients. Comparative studies have shown that Semaglutide is safe in clinical trials and three times more effective in weight reduction compared to other medications (Oliveira, 2022; Trabulsi et al., 2023). Its mechanism of action includes delaying gastric emptying, resulting in weight loss through caloric deficit, as well as reducing overall appetite and preference for high-fat foods (Van Der Aart-Van Der Beek, 2021). Among the most common side effects are gastrointestinal symptoms such as vomiting, diarrhea, and nausea, which contribute minimally to total weight loss—ranging from 0.07 to 0.5 kg (Medeiros et al., 2024).

Semaglutide, approved by the Food and Drug Administration (FDA) in 2017 for the treatment of type 2 diabetes and known for its weight loss effects, shares similarities with its predecessor, Liraglutide. However, due to its ability to bind to albumin, which reduces renal clearance, Semaglutide is more stable and has a longer half-life of approximately one week. Additionally, by stimulating glucose-mediated insulin secretion, reducing hepatic glucagon production, and slowing gastric emptying, this medication also helps suppress appetite. When combined with a low-carbohydrate diet and physical exercise, it can be highly effective in reducing body fat. A reduction in body weight was observed compared to baseline, with an average loss of 10.4 kg in individuals receiving the medication, while the placebo group experienced only a 0.4 kg reduction over a 20-week treatment period (Borges et al., 2023).

In a randomized clinical trial comparing the efficacy and adverse event profiles of subcutaneous Semaglutide administered once weekly at a dose of 2.4 mg versus Liraglutide administered once daily at a dose of 3 mg, the estimated average reduction in body weight was approximately −15.8% in

participants receiving Semaglutide, compared to −6.4% in those receiving Liraglutide. This indicates a difference of −9.4 percentage points in weight loss between the two medications. Despite the notable benefits associated with Semaglutide use for weight reduction, it is important to highlight that rebound effects may occur after discontinuation or reduced efficacy due to the persistence of unhealthy lifestyle habits, such as physical inactivity and an unbalanced diet (Lin et al., 2022). This occurs because weight loss in obese individuals is not a naturally physiological process; thus, the body may respond by increasing appetite, decreasing satiety, and tending to regain the original weight, potentially compromising the desired outcome (Hintze et al., 2023).

Table 2 - Comparative Data on Liraglutide and Semaglutide

Drug	Liraglutide	Semaglutide
Pharmacological Effects	Delays gastric emptying and promotes a prolonged sensation of satiety.	Delays gastric emptying and promotes a prolonged sensation of satiety.
Pharmaceutical Presentations	Adjustable-dose subcutaneous injectable systems up to 3.0 mg.	Subcutaneous injectable system of 0.25 mg or 1.0 mg; and oral tablets of 3 mg, 7 mg, or 14 mg.
Cost	Approximately R$616.00 per month.	Approximately R$1,000.00 per month.
Dosage	One daily subcutaneous injection, with weekly dose escalation up to a maximum of 3.0 mg per day.	One weekly subcutaneous injection, with dose escalation after four weeks.
Possible Adverse Effects	Nausea, vomiting, constipation or diarrhea, dyspepsia, gastritis, pancreatitis, hypoglycemia, and appetite loss.	Nausea, vomiting, constipation or diarrhea, dyspepsia, gastritis, pancreatitis, hypoglycemia, and appetite loss.

Source: Davies et al., 2018.

THE RELEVANCE OF THE PHARMACIST AS A HEALTH AGENT

Several chronic diseases and conditions are directly related to or negatively impacted by excess weight. Examples include type 2 diabetes mellitus, certain types of cancer, cardiovascular diseases, hypertension, and osteoarthritis. The onset or worsening of these and other conditions is primarily associated with pathophysiological processes involving increased oxidative stress and chronic inflammation. This phenomenon arises from the elevated demand for components necessary for mitochondrial energy production, which results in the generation of more harmful byproducts, such as reactive oxygen species. This establishes a vicious cycle that culminates in endothelial damage, insulin resistance, and dyslipidemia (Rains & Jain et al., 2011).

Despite the efficacy of these medications, misinformation spread through popular discourse can compromise their proper use. In this context, pharmacists play a crucial role, often serving as the final checkpoint to identify, correct, or mitigate potential risks associated with the use of these drugs. Pharmaceutical care is essential to ensure both efficacy and safety, encompassing the provision of information, guidance, and education on the correct use of medications. Furthermore, pharmacists should promote healthy lifestyle habits, contributing to the successful treatment of patients dealing with obesity (Rodrigues et al., 2018).

Pharmaceutical care is characterized by actions aimed at promoting, preventing, and restoring health, both individually and collectively, with a particular focus on the appropriate use of medications. This field encompasses a range of activities, from research and production to distribution, storage, prescription, and dispensing of medications. It is important to emphasize that medication dispensing is intrinsically linked to the need to provide accurate guidance on the proper use of these products (Publisi, 2019).

Lifestyle is closely linked to the occurrence of type 2 diabetes mellitus and metabolic syndrome, with obesity and physical inactivity significantly increasing this risk. Studies have shown that individuals who follow a diet rich in whole grains and polyunsaturated fatty acids, combined with reduced intake of trans fats and high-glycemic-index foods, are less likely to develop diabetes mellitus. Physical inactivity is as significant a risk factor for obesity as an inadequate diet and is directly associated with increased incidence of type 2 diabetes in adults, regardless of body mass index (BMI) or family history of diabetes mellitus (McLellan et al., 2007).

The pharmacist plays a vital role in providing pharmaceutical care to patients, aiming to identify and reduce potential drug-related problems (DRPs) that may arise due to various factors, such as healthcare system issues, individual patient characteristics, the nature of the disease and treatment, and socioeconomic conditions. These problems often result in negative clinical outcomes (NCOs), which are contrary to the intended therapeutic goals. Pharmaceutical care aims to promote health through simple actions such as health education, medication guidance, and the promotion of rational drug use, employing effective communication techniques. These measures have the potential to significantly improve the population’s quality of life (Oliveira et al., 2015).

Table 3 - Actions for the Practice of Pharmaceutical Care

Area	Description / Action
Pharmacotherapy Monitoring and Management	– Reduction and prevention of drug-related problems.
Health Education	– Enhances self-care among the population.
Management of Self-Limiting Health Problems	– Control of signs and symptoms.
Health Screening	– Pharmacovigilance. – Disease identification.
Dispensing	– Information and guidance to the patient or caregiver on the correct and safe use of medications.

Source: Rodrigues et al., (2018).

Pharmaceutical care involves direct interaction between the pharmacist and the patient, where the pharmacist encourages and raises awareness about the importance of the patient's understanding of the rational use of treatment. It also includes evaluating the safety and efficacy of the treatment for each individual, taking into account their clinical condition, personal and family medical history, concurrent medications, pregnancy, lactation, and age. Furthermore, the pharmacist must possess scientific knowledge about the treatment in order to provide guidance on usage, potential adverse effects, mechanisms of action, and necessary precautions. The pharmacist also plays a key role in encouraging the adoption of healthy lifestyle habits and in setting therapeutic goals to ensure successful treatment outcomes (Angonesi, 2008; Angonesi & Sevalho, 2010).

The pharmacist's role in managing patients with body mass index (BMI) disorders goes beyond simply evaluating treatment and providing guidance. It also involves promoting and integrating healthy lifestyle habits into the patient's daily routine. Considering that pharmacists are the most accessible healthcare professionals to the general population, it is essential that they establish a strong rapport with patients. This relationship fosters trust in the healthcare professional and enhances the effectiveness of the treatment (Kenny, 2020).

CONCLUSION

Obesity and overweight represent a complex global epidemic, placing a significant burden on healthcare systems such as Brazil's Unified Health System (SUS). GLP-1 analogues, initially developed for the treatment of type 2 diabetes, have emerged as an innovative approach to addressing this issue and its associated comorbidities. They are also increasingly considered by some as a weight loss strategy The growing prevalence of overweight adults and the rising incidence of type 2 diabetes underscore the urgency of effective weight management strategies. Obesity is not merely an aesthetic concern; it is associated with numerous complications, including cardiovascular diseases, psychological disorders, and musculoskeletal conditions, in addition to increasing healthcare costs. Appetite regulation, mediated by hormones secreted in the intestine and stomach, is fundamental to controlling food intake. However,

hormonal changes following weight loss make it difficult to maintain the new weight. GLP-1 analogues, such as Liraglutide and Semaglutide, act by promoting satiety, enhancing insulin sensitivity, and delaying gastric emptying, making them promising agents in the treatment of overweight. Nevertheless, the use of these medications must be accompanied by lifestyle changes, including a balanced diet and physical activity. When used in isolation, these treatments may lead to rebound weight gain after discontinuation. The supervision of healthcare professionals, including pharmacists, is essential to ensure the safety and efficacy of these treatments, which should be part of a long-term strategy to combat obesity and its complications.

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