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REVIEW ARTICLE

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Use of GLP-1 analogs in the treatment of obesity: an integrative and systematic review

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Abstract

Obesity is the global epidemic of the 21st century: about 1.5 billion adults worldwide are overweight, and among them, about 200 million men and 300 million women are obese. The prevalence of overweight and obesity is also increasing in children and adolescents in developed (about 25%) and developing countries (about 13%). Obesity has been associated with many comorbidities, including type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), hypertension, chronic kidney disease, cardiovascular disease (CVD), and malignancies, leading to increased mortality observed in obese individuals. Overweight and obesity were estimated to be associated worldwide with 3.4 million deaths, which could also be expressed as 4% of disability-adjusted life-years lost (DALYs). It is also alarming that children with severe obesity are apparently at in- creased risk of premature death. Managing obesity is hard and usually disappointing for both patients and physicians. Weight loss is difficult to achieve and even more difficult to sustain in the long term. When lifestyle modifications fail to achieve the predefined target, anti-obesity medications may be added on, as recommended by all relevant guidelines, including those of the Endocrine Society and recent guidelines for obese with diabetes. Glucagon-like peptide 1 (GLP-1) is an incretin secreted by L-cells in the intestinal mucosa and has been shown to act in the brain and periphery to cause effective weight loss. GLP-1 release is stimulated by food intake and its agonist, exenatide, is the first from the incretin family approved for weight-loss therapy by the Food and Drug Administration (FDA). In overweight and obese adults, it is concluded that the GLP-1 analogs and the Phentermine/Topiramate association proved to be among the best for the effects on weight reduction. Regarding childhood obesity, the FDA recently approved the use of Liraglutide. Schizophrenic patients, a target of studies due to risk factors, benefited from treatment with GLP-1 analogs.

Keywords: GLP-1 analogs. Obesity. Treatment.

Introduction

Obesity is a pathology with a multifactorial, chronic, and degenerative cause, currently considered one of the major causes of mortality and morbidities, as it is related to the difficulty, among health professionals and patients, encountered by the decrease in antiobesity medications and difficult adherence to treatment. by patients, in addition to the impact on Public Health, given that 40% of the entire world population is overweight **[1,2]**. Regarding epidemiology, there was a growing increase in the number of obese people between 2003 and 2019, respectively, from 12.2% to 26.8% **[3,4]**. During this period, female obesity increased from 14.5% to 30.2%, while male obesity increased from 9.6% to 22.8% **[5]**. In addition, it was shown that the prevalence of overweight increases with age, being highlighted in people between 25 and 39 years of age **[4,5]**.

In the last decade, there has been a considerable increase in cases of type 2 diabetes mellitus (T2DM) in the age group of children and adolescents and, concomitantly with this increase, the levels of obesity related to sedentary lifestyle, diet, and lifestyle habits. Since children and adolescents are not as successful concerning glycemic control and treatment adherence, this leads to the development of chronic complications more quickly, such as cardiovascular diseases. Although T2DM is linked to obesity and weight gain, some less favored ethnic groups have cases on the rise, because the pathophysiology is closely linked to genetic factors and not just lifestyle habits **[4,5]**.

Obesity in adults can be classified according to their current weight status and, consequently, their BMI, which is calculated by dividing weight by height squared. However, this calculation does not distinguish lean mass from fat mass and, therefore, does not reflect the distribution of body fat **[6]**. BMI is divided into classifications such as thin or underweight (BMI<18.5), normal or eutrophic (BMI 18.5-24.9), overweight or pre-obese (BMI 25-29.9), degree of obesity 1 (BMI 30-34.9), grade 2 obesity (BMI 30-39.9), grade 3 or morbid obesity (BMI ≥ 40) **[7]**.

The diagnosis can also be made by measuring the abdominal circumference, asking the patient in the supine position to inhale deeply, and, at the end of expiration, measuring the largest abdominal perimeter between the last rib and the iliac crest, in addition to of ultrasound to visualize visceral fat **[7]**.

The primary basis for the treatment of obesity is lifestyle intervention (diet and exercise), however, maintaining a long-term weight loss is a problem for many patients. Moderate body weight loss demonstrates clinically relevant benefits, including improved health-related quality of life, reduced cardiovascular risk, and reduced severity of obstructive sleep apnea **[3]**. Guidelines recommend the aid of pharmacological therapy in adults with a body mass index greater than or equal to 30, or greater than or equal to 27 in people with pre-existing comorbidities **[7]**.

There are 3 medullary mechanisms by which anti-obesity drugs produce their weightloss results: decreased nutrient absorption, increased energy expenditure, and appetite regulation. With the advancement of understanding the regulation of food intake and its respective metabolic pathways, the role of several intestinal peptides that act as key mediators has been the subject of interest in the development of pharmacological agents for appetite regulation **[8]**.

GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) receptor agonists are natural incretins, secreted by intestinal L-cells after ingestion of carbohydrates and fats, with the main function of regulating glycemia. GLP-1 stimulates glucose-induced insulin biosynthesis and secretion in pancreatic beta cells, through their proliferation and reduction of apoptosis **[9]**.

Consequently, it inhibits glucagon release by alpha cells and hepatic glucose production; in addition to prolonging gastric emptying time leading to the feeling of satiety. Studies have shown that GLP-1 is capable of reprogramming defective pancreatic beta cells, resulting in improved sensitivity to glucose, in addition to improved intestinal flora **[10]**.

The first GLP-1 receptor agonist described was exenatide, obtained through the structure of exendin-4, a natural peptide product isolated from the saliva of the lizard, Gila monster, native to Arizona and New Mexico, in the United States. Exenatide is a 39 amino acid peptide, with a longer half-life due to its resistance to DPP-4 degradation **[11]**.

Initially, the discovery of exendin-4 was not related to an incretin mimetic effect. The isolation of this natural product from the salivary gland of the Heloderma lizard took place in 1992, but it was only several years after the structural homology between exendin-4 and GLP-1, which induced insulin secretion through activation, was identified. directly from the GLP-1 receiver. This drug was approved by the FDA in the year 2005, and then by the EMEA in Europe in the year 2007 **[11]**.

Also, semaglutide, another GLP-1 agonist, approved by the FDA in 2021 for the treatment of obesity and overweight, is administered at a dose of 2.4 mg, once a week. Its main objective is weight loss, but it also demonstrates improvement in blood glucose and lipids. The efficacy of semaglutide in T2DM patients has also been demonstrated as an adjunct to other antidiabetic agents (eg metformin, thiazolidinediones, and sitagliptin) **[11]**.

Short-acting compounds, providing short-term receptor activation, comprise exenatide twice daily and lixisenatide once daily. Long-acting compounds, which activate the GLP-1 receptor continuously at the recommended dose, include once-daily liraglutide and once-weekly formulations of exenatide, albiglutide, dulaglutide, and taspoglutide. These different durations of action largely explain the variations among GLP-1RAs in their impact on fasting blood glucose (FBG), 24-hour glucose profile, and postprandial plasma glucose (PPG) levels. Delayed gastric emptying, for example, is more strongly associated with shortacting GLP-1RAs than longer-acting GLP-1RAs, and this may underlie the greater effects on PPG seen with short-acting GLP-1RAs. Meanwhile, the longer half-lives of the longeracting compounds allow for enhanced effects across the entire

24-h glucose level, including the FBG [12].

Also, longer-acting GLP-1RAs do not significantly affect gastric motility. Instead, they exert more of their effect through the pancreas, increasing insulin secretion and inhibiting glucagon secretion through the paracrine release of somatostatin [12]. Generally, the longer-acting GLP-1RAs improve glucose control via a downward shift of the entire 24- h glucose curve, which explains the greater overall efficacy compared with the short-acting exenatide twice daily. day and lixisenatide once a day [13-15].

Therefore, the present study analyzed the use of GLP-1 analogs in the treatment of obesity, as well as understanding the pharmacological aspects, identifying the studies of the respective drugs, identifying the benefits in childhood and adolescence, in patients with schizophrenia, and recognizing the secondary changes in obese patients.

Methods

Study Design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

Data Sources and Research Strategy

This study had descriptive–exploratory, qualitative characteristics, through a bibliographical review of national and international articles. The research was carried out in the year 2022 in the Scielo, Pudmed, and The Lancet databases.

Study Quality and Risk of Bias

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

Results and discussion

Resume of Findings

A total of 128 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 64 articles. A total of 52 articles were fully evaluated and 40 were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies at high risk of bias and 43 studies that did not meet the GRADE.

Figure 1. Flowchart showing the article selection process.

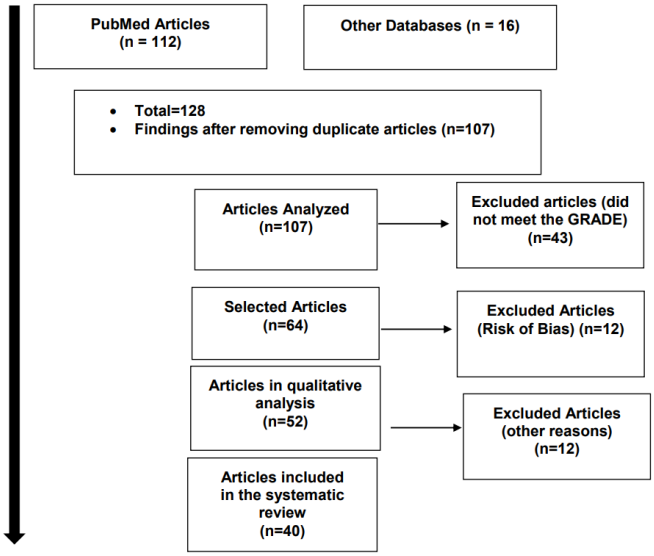
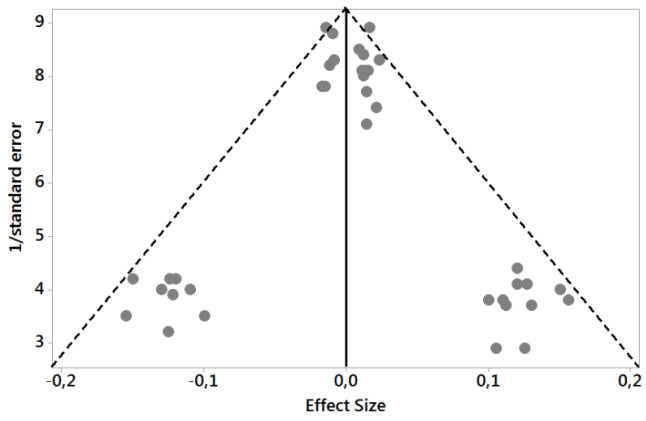


Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are presented in the upper region.

Figure 2. The symmetrical funnel plot suggests no risk of bias between the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (NTotal=40 studies evaluated in full in the systematic review).



Major Clinical Findings

Energy balance, eating, and appetitive behaviors are highly regulated by central and peripheral hormones

and neuropeptides that act on multiple brain areas and peripheral organs **[16,17-19]**. Nervous system (CNS) networks are involved in the development and control of obesity in humans, including the hypothalamus, reward system, emotion and memory-related brain areas, along with the attention cortex and prefrontal cortex responsible for cognitive control. **[19]**. Pathways that control energy balance and predisposing factors to obesity may vary between humans and other species and are described in detail in other articles in the current special issue of "Obesity".

In this context, FDA-approved drugs and new therapies under investigation in preclinical studies and clinical trials exert their anti-obesity effects through one or more of the following mechanisms: 1) decreased appetite and caloric intake, 2) increased energy expenditure, 3) decreased fat absorption **[18,19]**.

Adipose tissue produces free fatty acids, hormones, and cytokines, such as leptin, resistin, visfatin, interleukin-6, tumor necrosis factor, plasminogen inhibition activating factor, angiotensinogen, among others **[20,21]**. Since some of these produced substances participate in the regulation of body weight, such as leptin, in which its serum level is proportional to the amount of body fat and the circulating level is pulsatile, with peaks during the night, exerting an anorectic effect, through the hypothalamic arcuate nucleus, leading to decreased food intake and increased energy expenditure **[22]**.

Adiponectin is an anti-inflammatory adipokine produced by adipose tissue, being one of the insulin sensitizers, its levels are inversely proportional to adiposity and insulin resistance. Therefore, adiponectin is related to a decrease in serum glucose levels and a reduction in insulin resistance **[22]**.

Some hormones are involved with satiety, such as glucagon-like peptide (GLP-1), which is mainly secreted by enteroendocrine cells of the gastrointestinal tract, in response to the presence of nutrients in the lumen of the small intestine. It works by inhibiting gastric emptying and thus promoting a feeling of prolonged satiety **[21]**. Cholecystokinin is an intestinal peptide, released by I cells of the gastrointestinal tract, which acts on satiety, mainly prandial. Therefore, it inhibits food intake and induces pancreatic biliary secretion and vesicular contraction. Furthermore, ghrelin is synthesized by stomach cells, usually before meals, performing orexigenic actions in the hypothalamus, stimulating food consumption, in addition to stimulating gastric emptying and reducing gastric acid secretion. In obese people, the levels of this hormone after a meal remain high for a longer time **[21]**.

It is known that adipose tissue and the intestine play a key role in the secretion of several chemical mediators that modulate appetite, insulin action, and inflammatory responses. The intestinal microbiota is a complex community of bacteria present in this system. Its diversity and functionality depend on several factors, which include, for example, dietary patterns, the use of medications, and antibiotics. In obesity, this microbiota changes, increasing the inflammatory process and insulin resistance; the relative increase of bacteria of the genus Firmicutes is positively correlated with body fat, and waist circumference, and negatively with muscle mass **[23]**.

Because of recent publications in the area of metabolic diseases, the role of GLP-1 analogs has been increasingly studied to improve the treatment of obesity. Endogenous GLP-1 is a polypeptide formed by 31 amino acids, synthesized and secreted by epithelial L cells of the small intestine. Its interaction with the GLP-1 receptor predominates in the upper intestinal tract, pancreatic islets, and visceral afferent nerves. The LP-1 receptor can be found in the central nervous system responsible for regulating caloric intake **[24]**. After GLP-1 is secreted, there is a response to the increase in glycemic levels after meals, acting on the pancreatic islets, promoting greater insulin release, and on alpha cells. This incretin can reduce blood glucose and increase liver and muscle sensitivity to insulin. GLP-1 acts in the CNS and Peripheral Nervous System to regulate appetite **[24]**.

Randomized studies have shown that Liraglutide at a dose of 3 mg per day is effective in trials and proved to be more effective than other drugs used in the treatment of obesity that is not GLP-1 agonists. The Phentermine/Topiramate association brought more results than Liraglutide. Dulaglutide showed a reduction in HbA1c compared to the respective baselines. Albiglutide demonstrated effectiveness in promoting weight loss. All the drugs mentioned are safe and effective therapeutic options if used continuously and in conjunction with diet and physical exercise **[14]**.

Further, Dulaglutide is the drug most recently approved by the FDA, in 2014, it contains the GLP-1 sequence modified and coupled through a spacer peptide, to the Fc domain of the human immunoglobulin IgG4, it is administered once a week it has a positive effect in terms of reducing body mass index and waist circumference, but most authors describe a modest effect on weight loss that depends on the administered dose; and Albiglutide includes two units of GLP-1 modified in its cleavage site by serine protease DPP-4, which are linked to human serum albumin protein **[14]**.

In addition, the Liraglutide Satiety and Clinical Adiposity program is included in four phases 3 studies of

approximately 5,000 overweight participants (BMI ≥27 kg/m 2) with comorbidities and obesity (BMI ≥30 kg/m 2), divided into placebo and using liraglutide 3.0 mg. Across studies, weight loss over 56 weeks was between 6.2 kg and 8.4 kg with liraglutide compared with 0.2 to 2.8 kg with placebo. Liraglutide together with lifestyle changes resulted in weight loss of 8.4 ± 7.3 kg compared to 2.8 ± 6.5 kg in the placebo group over these weeks. Overall, 63% and 33% of the population in the liraglutide 3.0 mg group had ≥5% and ≥10% weight loss, respectively, compared to 27% and 11% in the placebo group, respectively. Published effects from the SCALE Maintenance study, which enrolled obese or overweight participants who had already lost ≥ 5% of their baseline weight, showed that liraglutide maintained the weight lost during the run-in and further stimulated weight loss of ≥ 5% at ≥ 10% **[25]**.

Also, semaglutide Treatment Effect in People with Obesity (STEP) is a global program, carried out in 129 sites in 16 countries in Asia, Europe, North America, and South America, phase 3 aims to evaluate the efficacy and safety of semaglutide administered via subcutaneously at doses higher than those prescribed for the treatment of type 2 diabetes in adults (18 years of age or older), once a week in overweight and obese persons, with or without weight-related complications. This 68-week, randomized, double-blind study, by comparing the placebo and the use of semaglutide, associated with lifestyle changes, analyzed its outcomes in overweight or obese adults without diabetes. In conclusion, it was observed that in the semaglutide group, participants were more likely to lose 5% to 20% or more of baseline body weight at week 68 than those receiving a placebo. Change in body weight from baseline to week 68 was -15.3 kg in the semaglutide group compared to -2.6 kg in the placebo group, waist reduction –13.54 cm with semaglutide compared to –4, 13 cm with placebo, BMI -5.54 with semaglutide compared to -0.92 with placebo. Regarding the safety profile and side effects, similar percentages were reported between both groups, 89.7% in the groups using semaglutide and 86.7% in the placebo group. Among the most evident side effects were gastrointestinal disorders such as nausea, diarrhea, vomiting, and constipation of mild to moderate severity, transient and resolved without a permanent break from the regimen **[26]**.

In addition, a retrospective observational study carried out at the diabetes clinic of the S. Camillo Forlanini Hospital in Rome aimed to evaluate the impact of semaglutide concerning metabolic control, cardiovascular risk, dietary behavior, and efficacy of DM 2 treatment showed that the drug was effective in reducing glycated hemoglobin, fasting glucose, blood pressure, and lipid profile in patients using it for 32 weeks **[2]**. Glycated hemoglobin (HbA1C) levels were reduced by 1.38%, fasting blood glucose by 56.53 mg/dl, and weight by 6.03 kg, on average. Systolic and diastolic blood pressure, total cholesterol, HDL, LDL, and triglycerides improved concomitantly **[2]**.

A meta-analysis on the efficacy and safety of the glucagon-like peptide agonist semaglutine in patients with type 2 diabetes mellitus indicated that oral semaglutide is superior to placebo in terms of change in HbA1c, change in body weight, change in FG, change in GPSM, number of participants achieving HbA1c < 7.0%, all-cause death, and SAEs. Oral semaglutide is superior to other AHAs in terms of change in HbA1c, change in body weight, change in SMPG, and the number of participants achieving HbA1c < 7.0%. Finally, oral semaglutide did not increase the incidence of AEs, hypoglycemia (severe or symptomatic confirmed by BG), stroke, heart failure requiring hospitalization, or stroke compared with placebo or other AHAs. Oral semaglutide has a stronger hypoglycemic effect than placebo or other AHAs and similar safety **[27]**.

Furthermore, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are a new class of AHAs that are recommended by the ADA/EASDs. However, many patients are reluctant to use GLP-1 ARs due to fear of injectable therapies. For these patients, oral semaglutide may represent an alternative option for early initiation of GLP-1 Ras treatment **[27]**.

Renal failure is a frequent comorbidity in patients with T2DM and can affect the metabolism and excretion of anti-diabetic drugs, which makes achieving treatment goals challenging. Many antidiabetic drugs, including metformin and insulin, are primarily eliminated by the kidneys and therefore require dose adjustments or are contraindicated in patients with chronic kidney disease. In contrast, the GLP-1 ARs liraglutide, semaglutide, albiglutide, and dulaglutide are rarely cleared by the kidney and do not require dose adjustment in patients with stage 4 and above chronic kidney disease and may be useful alternatives to other hypoglycemic drugs. Oral semaglutide was effective in patients with type 2 diabetes and renal failure providing a new treatment option for this population. Compared with placebo and other AHAs, oral semaglutide leads to improvements in glycemic control and weight control and a significantly lower rate of hypoglycemia in T2DM patients. These findings indicate that oral semaglutide may be a safer and more effective option for T2DM patients than liraglutide, dulaglutide, empagliflozin, and sitagliptin **[27]**.

Studies regarding the use of exenatide have shown

significant effectiveness in weight loss. In a group of 152 obese individuals, a randomized study was performed comparing the use of exenatide 10 ug versus placebo for 24 weeks, demonstrating that the group using the GLP-1 analog lost 5.1 kg from baseline versus 1.6 kg of the placebo. Clinical trials with exenatide in patients with type 2 diabetes showed a reduction in body weight of 3 kg in twenty-four weeks and 5.3 to 5.7 kg in three years of treatment, and when associated with lifestyle changes, there was a reduction of 6,16kg **[28]**.

A systematic review and meta-analysis study included adults with type 2 diabetes, excluding patients with chronic kidney disease, and used albiglutide, dulaglutide, exenatide, semaglutide, and taspoglutide once a week, in addition to the control drug (placebo). Participants were required to report data on cardiometabolic outcomes (HbA1c, fasting blood glucose, body weight, SBP, DBP, HR, CRP, and lipid profile). As a primary outcome of glycated hemoglobin, the meta-analysis showed different effects of GLP1 given once a week compared to placebo. Direct evidence demonstrated an average reduction of 1.4% in HbA1c. When compared between GLP1 analog drugs, it shows a greater reduction in HbA1c values with Dulaglutide 1.5 mg compared to Dulaglutide 0.75 mg, Albiglutide 10 mg, and Taspoglutide 20 mg, while no difference was seen compared to Exenatide **[29]**.

Also, a systematic review and meta-analysis study included adults with type 2 diabetes, excluding patients with chronic kidney disease, and used albiglutide, dulaglutide, exenatide, semaglutide, and taspoglutide once a week, in addition to the control drug (placebo). Participants were required to report data on cardiometabolic outcomes (HbA1c, fasting blood glucose, body weight, SBP, DBP, HR, CRP, and lipid profile) **[30]**.

As a primary outcome of glycated hemoglobin, the meta-analysis showed different effects of GLP1 given once a week compared to placebo. Direct evidence demonstrated an average reduction of 1.4% in HbA1c. When compared between GLP1 analog drugs, it shows a greater reduction in HbA1c values with Dulaglutide 1.5 mg compared to Dulaglutide 0.75 mg, Albiglutide 10 mg, and Taspoglutide 20 mg, while no difference was seen compared to Exenatide **[30]**.

Regarding secondary cardiometabolic results, the study showed that fasting glycemia suffered a greater reduction with Exenatide when compared to placebo, followed by Dulaglutide 1.5 mg, Taspoglutide 20 mg, Dulaglutide 0.75 mg and Albiglutide. As for body weight, the results of the meta-analysis showed a significant reduction of 1.3 kg in the use of GLP1 analogs. Administration once a week showed no significant effect on BP, total cholesterol, and C-reactive protein. Marginal differences were demonstrated for low-intensity lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and PAS. Exenatide increased heart rate compared to the others **[31]**.

Lixisenatide, which was approved in 2013 only in the European Union, is an analog of exenatide with a prolonged half-life due to the introduction of six terminal lysine residues in the peptide chain of the natural product **[27]**. A survey was carried out comparing obese or overweight individuals who adhered to lifestyle changes and used medication to reduce weight. Some adverse reactions were observed that caused patients to give up treatment, weight regain and change their quality of life score. The main adverse effects observed but not crucial were: gastrointestinal events, depressive events, and anxiety. In the research result, it was observed that all drugs except levocarnitine reduced body weight, with phentermine-topiramate and GLP-1 receptor agonists proving among the best. All drugs except pramlintide were associated with a greater proportion of participants reducing their body weight by 5% or more compared with lifestyle modification alone. All drugs except metformin, SGLT2 inhibitors, and pramlintide caused a greater proportion of participants to reduce weight. Phentermine-topiramate, GLP-1 receptor agonist and naltrexone-bupropion were shown to be among the most effective in reducing body weight by 5% or more and 10% or more. No evidence of weight regain after discontinuation of treatment was seen, however, only 3 studies provided data on weight changes either at end of treatment or at follow-up and none of the three reported body weight change since the end of treatment. medication until the end of follow-up with associated estimates of variability **[30]**.

In addition, network nodes included phentermine-topiramate, naltrexonebupropion, GLP-1 receptor agonists, orlistat, and lifestyle modification alone. Except for orlistat, all three of these drugs improve quality of life. One study suggested a statistically significant increase in depression symptom scores in people who received naltrexone bupropion. The study team was unable to identify evidence addressing body image or anxiety symptom scores **[30]**.

Besides, phentermine-topiramate represents a well-established weight reduction treatment that is approved for this indication in the US only. Intermediate risk of adverse events leading to treatment discontinuation. The suggested dose of semaglutide for weight loss is 2.4mg per week which is notably higher than the suggested dose of 1.0mg per week for the treatment of type 2 diabetes. once a week, which greatly improves treatment adherence. However, other once-

weekly GLP-1 receptor agonists such as dulaglutide and once-weekly exenatide did not show similar effects on absolute weight reduction [30].

Orlistat is widely used for weight loss worldwide, but possibly not better than lifestyle modification alone in our study. However, orlistat lowers LDL cholesterol more than MID, which may favor its use in patients with hyperlipidemia. Metformin and SGLT2 inhibitors have been evaluated as candidates for weight reduction because of their effects on weight in people with diabetes. However, in the present analysis, the weight reduction effects of these drugs proved to be less than the MID weight loss threshold. Furthermore, metformin is associated with gastrointestinal adverse events and SGLT2 inhibitors increase the risk of genital infection and ketoacidosis [30].

In conclusion, phentermine topiramate and GLP-1 receptor agonists are among the best for weight reduction effects in overweight and obese adults as an adjunct to lifestyle modification. Semaglutide, in a posthoc analysis, showed significantly greater weight loss than the other investigated drugs. Phentermine-topiramate and naltrexone-bupropion result in the most adverse events. Moderate or high certainty evidence for most comparisons requires credible application of these findings as guides to clinical practice [30].

Also, improvements in systolic blood pressure (SBP) and diastolic blood pressure (DBP) have been reported in clinical trials of GLP-1RAs. Indeed, a meta-analysis of trials involving once-weekly exenatide, twice-daily exenatide, or liraglutide found that these treatments significantly lowered SBP: by -1.79 and -2.39 mmHg compared to placebo and active controls. A meta-analysis of studies involving once-weekly exenatide, twicedaily exenatide, or liraglutide found that these treatments increased heart rate by 1.86 beats/min (bpm) versus placebo and by 1.90 bpm versus active comparators. Comparative trials have suggested that increases in heart rate may be less with twice-daily exenatide than once weekly exenatide or liraglutide. Dulaglutide is also associated with a small increase in heart rate, similar to that of liraglutide. Lixisenatide and albiglutide do not appear to be associated with clinically relevant increases in heart rate [32].

Finally, most GLP-1 receptor agonists are administered subcutaneously, with the advantage of weight loss when treatment is prolonged. Despite this, there are some adverse effects such as gastrointestinal, including nausea and vomiting, in addition to reports of the association of these drugs with the onset of pancreatitis in some patients [32].

Child Obesity

Childhood obesity is considered a global public health problem. In childhood, obesity is associated with greater risks of developing type 2 diabetes mellitus, sleep apnea, hypertension, polycystic ovary syndrome, mental disorders, and orthopedic pathologies. The first-line treatment is the practice of physical exercise and dietary control, but depending on the case, the addition of drug treatment is necessary. In the United States and the European Union, drug treatment is limited to Orlistat and Phentermine for adolescents older than 12 and 16 years, respectively. Treatment for childhood T2DM in most countries is limited to Metformin and insulin [27,33].

The incretin hormones, GLP1 and GIP, are of potential interest for drug therapy, acting significantly on insulin secretion and glucose tolerance in individuals with T2DM. In addition, GLP1 delays gastric emptying promotes satiety, and reduces food intake, contributing to weight loss. Recently, the US Food and Drug Administration (FDA) approved the use of the GLP1 agonist (Liraglutide) for children [33].

A study carried out through randomized controlled trials on the effectiveness of GLP1 agonists in T2DM, pre-diabetes, and obesity in children < 18 years of age showed a reduction in HbA1c by 0.3% compared to control studies. However, GLP1 agonist therapy reduced weight mainly in children with obesity (2.74 kg reduction) when compared to obese children with T2DM (0.97% reduction). In addition, some adverse effects were found such as gastrointestinal symptoms and minor hypoglycemic episodes. The randomized trial concluded that GLP-1 agonists are effective in the treatment of children with obesity and/or type 2 diabetes mellitus [34].

Obesity in Patients with Schizophrenia

Patients diagnosed with schizophrenia have an increased risk of developing the cardiometabolic disease due to factors such as genetic predisposition, reduced physical activity, poor diet, and the use of antipsychotic medications. Weight gain results in greater difficulty in the line of treatment for this population, however, due to the difficulty in changing lifestyle and the adverse effects of drugs used to combat obesity, they lead to a major barrier in combating weight gain. Weight. As a result of these limitations, and with new studies regarding glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of obesity, there has been an interest in research associating GLP-1 analogs with clozapine and olanzapine aimed at for patients with schizophrenia [13].

Three studies were carried out in Australia and

Denmark, lasting an average of 12 to 24 weeks, two of which used exenatide 2mg subcutaneously once a week and the last one used liraglutide 1.8mg subcutaneously once a day. One study restricted only clozapine and olanzapine as an antipsychotic, another to clozapine alone, and the third to clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpride, and sertindole. Two studies were blinded and placebo-controlled, while the third was open-label. All studies included patients with schizophrenia, male adults aged between 18 and 65 years, with a mean BMI of 35.4kg/mg² and with data on body weight, fasting glucose, HDL, triglycerides, systolic blood pressure, and diastolic and HbA1c. One study included patients with type 2 DM, while the others excluded such specificity. Furthermore, one study required patients to have impaired glucose tolerance **[13]**.

From the data analysis, it is concluded that the use of GLP-1 treatment for weight control in patients with schizophrenia using clozapine or olanzapine is very promising. The mean weight loss between the intervention and control groups was 3.71 kg less for the intervention groups. Decreases in waist circumference, BMI, LDL, fasting blood glucose, HbA1c, and visceral fat were all significantly different between treatment and control. In terms of side effects, nausea was the most common in the GLP-1 group, but it did not interfere with the weight regression model. Furthermore, there are no risks of drug interactions, as GLP-1 is not hepatically metabolized by cytochrome P450, thus not altering the elimination of antipsychotics. Another benefit found concerns the form of subcutaneous administration and weekly frequency, which results in greater adherence and ease of treatment for these patients **[13]**.

When comparing existing drugs, so far Liraglutide 3 mg has proved to be the most effective and effective in trials for the treatment of obesity with GLP-1 analogs. Phentermine, an amphetamine derivative, in association with Topiramate, an anticonvulsant used as a mood stabilizer, brought more proven results than Liraglutide. Dulaglutide, a drug recently approved by the FDA, showed a significant reduction in glycated hemoglobin in the patients under study and Albiglutide demonstrated proven efficacy in promoting weight loss. Such cited drugs are safe and effective for the treatment of obesity when associated with non-pharmacological forms such as physical activity and diet **[13]**.

Phentermine plus Topiramate represents a well-researched weight loss treatment that is only approved in the United States. Oral semaglutide, popularly known as Ozempic, an analog of the glucagon-like peptide 1 receptor (GLP-1Ras), was recently studied, proving its effectiveness in reducing glycated hemoglobin, fasting glucose, blood pressure, and lipid profile in patients in an observational study retrospective. Such a drug may be a safer and more effective option for obese patients with type 2 diabetes mellitus than Liraglutide, Dulaglutide, Empagliflozin, and Sitagliptin **[35]**.

Glucagon-like peptide-1 (GLP-1) receptor agonists are a new class recommended by the ADA/EASDs, but many patients are reluctant to use them for fear of injectable therapies, so oral semaglutide may be an alternative option for the start of treatment. Exenatide has demonstrated significant efficacy in weight loss, supported by a randomized trial. Regarding secondary cardiometabolic results, fasting blood glucose was significantly reduced with the use of the drug. In contrast, exenatide showed an increase in heart rate when compared to other drugs in the same class. Lixisenatide, approved only in the European Union, is an analog of exenatide with a prolonged half-life **[36]**.

Some adverse effects of the use of GLP-2 analogs were presented, including gastrointestinal events, depressive events, and increased anxiety. A proven advantage of GLP-1Ras is that they are rarely eliminated by the kidneys and do not require dose adjustment in chronic renal patients, unlike some antidiabetic drugs such as metformin and insulin. Most GLP-1 receptor agonists are administered subcutaneously, with the advantage of weight loss when treatment is prolonged. Despite this, there are some adverse effects such as gastrointestinal, including nausea and vomiting, in addition to reports of the association of these drugs with the onset of pancreatitis in some patients **[37]**.

In this sense, Orlistat is widely used for weight loss worldwide and also acts to reduce LDL cholesterol, favoring its use in patients with dyslipidemia. Metformin and SGLT2 inhibitors have been evaluated in studies and have proven to be inferior to other drugs in terms of weight loss. Furthermore, Metformin is associated with gastrointestinal adverse events and SGLT2 inhibitors increase the risk of genital infection and acidosis **[38]**.

Thus, in overweight and obese adults, it was concluded that GLP-1 analogs and the Phentermine/Topiramto association were among the best for weight reduction effects. Regarding childhood obesity, drug treatment is limited to Orlistat for adolescents over 12 years of age and Phentermine for those over 16 years of age in the United States and the European Union. In addition, T2DM treatment in most countries for this population is limited to metformin and insulin. Recently, the US FDA approved the use of Liraglutide for children to delay gastric emptying, promote satiety and reduce food intake, contributing to weight loss. The adverse effects found are the same as

in adults [38].

In this sense, schizophrenic patients, an audience at increased risk for cardiometabolic diseases due to genetic predisposition, use of antipsychotic drugs, and difficulty in changing their lifestyle, are also targets of studies. From the data analysis, it was found that treatment with GLP-1 for weight control in patients using Clozapine or Olanzapine is promising, proving the decrease in abdominal circumference, BMI, LDL, fasting glucose, HbA1c, and visceral fat. The most common side effect among this group is nausea, but it did not interfere with the weight regression model [39,40].

Conclusion

Through the retrospective studies presented, it is concluded that GLP-1 analogs are widely targeted in the treatment of obesity, because it acts on the central and peripheral nervous system to regulate appetite, in addition to other benefits such as the reduction of blood glucose and the increased liver and muscle sensitivity to insulin action.

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The authors declare no conflict of interest.

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