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Review article

Effects of Orforglipron in the treatment of obesity: systematic review and meta-analysis

Efeitos do Orforglipron no tratamento da obesidade: revisão sistemática e metanálise

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Abstract

Objective: to conduct a systematic review and meta-analysis on the efficacy of Orforglipron in the treatment of obesity. **Materials and Methods:** a search was conducted in the Virtual Health Library (VHL), SciELO, and PubMed databases using the descriptors "Orforglipron" and "Obesity," chosen based on MeSH (Medical Subject Headings) terms. Inclusion criteria encompassed randomized clinical trials published between 2023 and 2024 regarding the use of Orforglipron in obesity treatment. Studies with different designs, such as systematic reviews and author response letters, studies involving other current anti-obesity drugs, and works incompatible with the stated objective were excluded. For the meta-analysis, a fixed-effect model and heterogeneity tests were used, specifically Cochran's Q test and I^2. The analysis assessed absolute weight loss using a daily dose of 45 mg of Orforglipron versus placebo. **Results:** five randomized clinical trials were selected. A meta-analysis of two studies with a 45 mg dose of Orforglipron revealed a statistically significant average weight loss of 7.7 kg. **Conclusion:** further studies with larger sample groups are necessary to determine functional therapeutic protocols.

Keywords: Pharmacological Treatment. Obesity. GLP-1 receptor.

Resumo

Objetivo: realizar uma revisão sistemática e metanálise sobre a eficácia do Orforglipron no tratamento da obesidade. **Materiais e Métodos:** foi realizada uma busca nas bases de dados Biblioteca Virtual de Saúde (BVS), SciELO e PubMed, com os descritores “Orforglipron” e “*Obesity*”, escolhidos com base nos termos técnico-científicos MeSH (*Medical Subjective Heading*). Os critérios de inclusão abrangeram ensaios clínicos randomizados publicados entre 2023 e 2024 acerca do uso de Orforglipron no tratamento da obesidade. Foram excluídos trabalhos de diferentes delineamentos, como revisões sistemáticas e cartas de respostas dos autores, estudos envolvendo outros fármacos antiobesidade atuais e trabalhos incompatíveis com o objetivo supracitado. Para a confecção da metanálise, foi utilizado modelo de efeito fixo e testes de heterogeneidade e para a análise de heterogeneidade, foi utilizado o teste Q de Cochran e o I^2. Foi avaliada a perda de peso absoluta por meio do uso do Orforglipron dose de 45 mg diária *versus* placebo. **Resultados:** foram selecionados cinco ensaios clínicos randomizados. Uma metanálise de duas pesquisas com dose de 45 mg de Orforglipron revelou uma perda média de 7,7 kg com significância estatística. **Conclusão:** novos estudos com grupos amostrais mais amplos são necessários para determinar protocolos terapêuticos funcionais.

Palavras-chave: Tratamento Farmacológico. Obesidade. Receptor de GLP-1.

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Introduction

For the World Health Organization (WHO) and the Brazilian Society of Endocrinology and Metabolism (SBEM), obesity consists of excess fat in the body, as well as quantity that determines damage to health. There are multiple mechanisms to calculate and/or estimate the body composition of an individual, being the Body Mass Index (BMI) one of the most used tools. This calculation is made from the ratio between weight and height squared (kg/m^2) and, despite its limitations in terms of accuracy in body composition, it is a good predictor of obesity. A healthy BMI ranges from 18.5 kg/m^2 to 24.99 kg/m^2. Values below 18.5 kg/m^2 indicate an individual below ideal weight; between 25 kg/m^2 and 29.99 kg/m^2 indicate overweight; 30 kg/m^2 and 34.99 kg/m^2 indicate obesity grade I, 35 kg/m^2 to 39.99 kg/m^2 indicate obesity grade II and values above 40 kg/m^2 indicate obesity grade III (morbid obesity), according to Chart 1[1].

Chart 1. Body Mass Index.

Body Mass Index	Classification
< 18.5	Below weight
18.5 – 24.99	Ideal weight
25 – 29.99	Overweight
30 – 34.99	Obesity grade I
35 – 39.99	Obesity grade II
> 40	Obesity grade III

Source: Brazilian Association for the Study of Obesity and Metabolic Syndrome[1].

The WHO estimates that by 2025, about 2.3 billion people in the world will be overweight, and 700 million individuals will have some degree of obesity[2]. Moreover, according to the Ministry of Health, the prevalence of obesity in Brazil is 20.3%, an increase of 72% compared to 2006 and almost 300% compared to 1975[2]. Currently, 55.4% of Brazilians are overweight, with more overweight in men (57.1%) than women (43.9%)[2]. Regarding childhood obesity, the Pan American Health Organization highlights that 12.9% of Brazilian children between 5 and 9 years old are obese, as well as 7% of adolescents between 12 and 17 years[2].

Obesity is a chronic disease that directly influences endocrine-metabolic factors, which increases the risk for brain and cardiovascular diseases such as Systemic Arterial Hypertension (SAH), Diabetes Mellitus type 2 (DM2), Metabolic Syndrome, Cerebrovascular Accident (CVA) and Acute Myocardial Infarction (AMI)[3-12]. In this scenario, anti-obesity pharmacological treatment is often necessary and is indicated for patients with BMI > 30 kg/m^2 without comorbidities or BMI > 27 kg/m^2 with comorbidities such as DM2 or SAH.

In the first analysis, today, there are only two GLP-1 (Glucagon Like Peptide-1) agonists approved and used in the pharmacological treatment of obesity: Liraglutide 3mg and Semaglutida

2.4mg. However, given the difficulty of access and manipulation of these medications, in 2022, a new GLP-1 agonist was studied for weight and blood glucose reduction in overweight patients, obesity and DM 2. The drug LY3502970 – commercially known as Orforglipron– has great potential, given that it is a non-peptide medication for oral daily use, therefore being less expensive and easier to manage by the patient[8].

Currently, despite extensive research and the multiple therapeutic approaches available on obesity treatments, the effectiveness of current protocols is questionable due to the high associated side effects, the onerous nature of treatment and the high rate of failure in long-term treatment[2,12,13].

In this sense, the objective of this work is to perform a systematic review and meta-analysis of the literature to evaluate the effectiveness of Orforglipron – new GLP-1 agonist drug – regarding the treatment of obesity.

Materials and Methods

This is a systematic literature whose guiding question was: "Is Orforglipron use in the treatment of obesity superior to placebo?".

In this context, the therapeutic audience included overweight and obese adults with or without overweight comorbidities – such as SAH and DM 2. The control population in this systematic review was composed of healthy individuals, who were investigated for comparative purposes. The anti-obesity intervention was considered the administration of any dose of Orforglipron (fixed or ascending), and the results evaluated about weight loss were qualified and quantified.

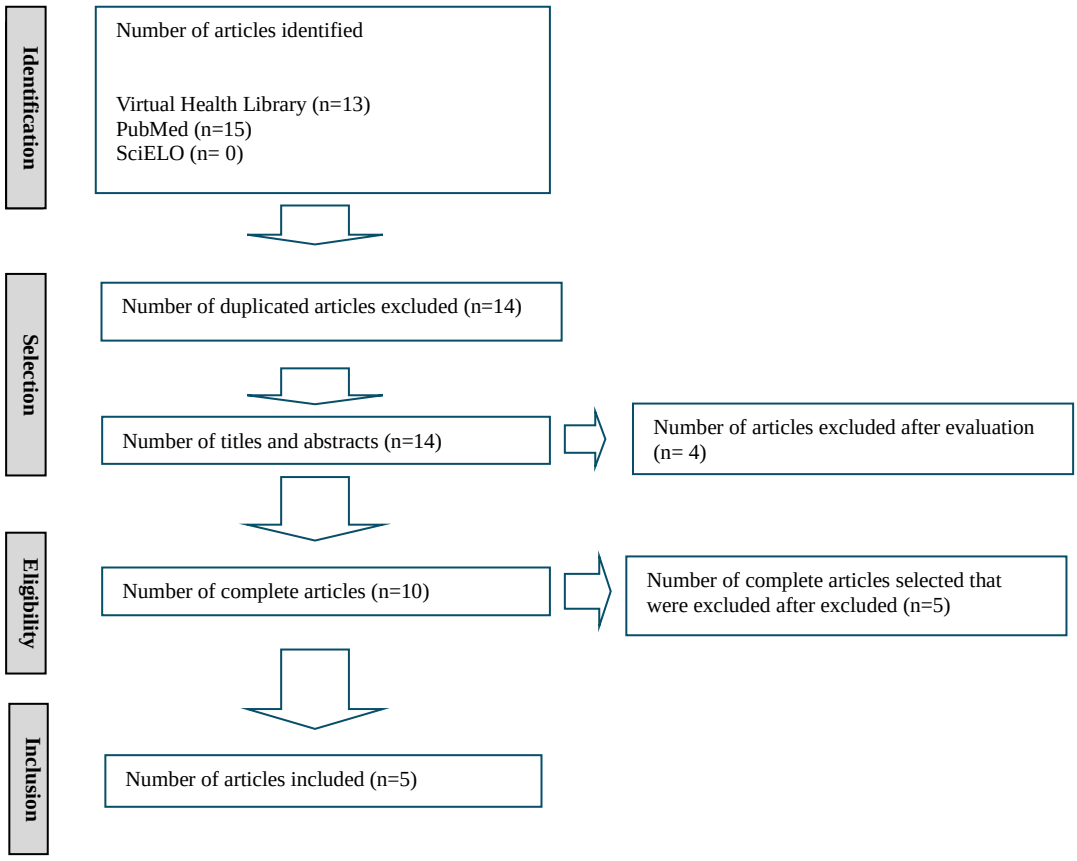
Therefore, a careful search was carried out on 03/04/2024, through the Virtual Health Library (VHL), SciELO (Scientific Electronic Library Online) and PubMed databases, with the descriptors “Orforglipron” and “Obesity”, chosen based on the technical-scientific terms MeSH (Medical Subjective Heading). Furthermore, the Boolean operator “AND” was incorporated. Regarding filters, “English”, “Meta-Analysis”, “Clinical Trial” and “Randomized Controlled Trial” were included.

The inclusion criteria included randomized clinical trials in 2023 and 2024 on the use of Orforglipron in the treatment of obesity. Studies from different designs were excluded, such as systematic reviews and letters of response from the authors; studies involving other current anti-obesity drugs and works incompatible with the aforementioned objective, totaling, at the end, five articles to compose the discussion of this review.

As a result, thirteen articles were found in the VHL, zero articles in SciELO and fifteen articles in PubMed, of which many were duplicated and, as a result, two articles from the VHL and twelve articles from PubMed were excluded. Then, a judicious reading of the title, keywords and abstract of the remaining papers was carried out, with a view to selecting the articles with greater compatibility to the theme proposed in this article. Thus, three articles from the VHL and one article from PubMed were excluded, totaling ten papers for screening in the inclusion criteria.

During data collection, the feasibility of using some publications was questionable. Thus, the third author MJSM was activated and was responsible for defining this conjuncture. Five papers composed the final sample for this systematic review. Flowchart 1 below demonstrates the methodology of this work.

Flowchart 1. Search strategy in the databases.



For the preparation of the meta-analysis, fixed effects models and heterogeneity tests were used. Regarding the heterogeneity analysis, the Q test of Cochran and I^2 was used. For the calculation of weight or contribution of each study, models of random effects were used. In this case, the weights were assigned based on both variability within the studies and between the studies. The Funnel Plot was not used to investigate the presence of publication bias or selective bias in the studies included in the meta-analysis, since less than 10 studies were obtained for the meta-analysis. The confidence interval used was 95% and significant p-value <0.05. The meta-analysis evaluated absolute weight loss by using Orforglipron at a daily dose of 45 mg versus placebo. The calculations were processed using the tool Meta-mar version 3.5.1.

The work of Pratt *et al*. was not used in the meta-analysis calculations because of the lack of data available in the placebo group, despite having a study arm that used 45 mg of the medication[11]. Another important point is to consider that Frias *et al*.[9] evaluated the data at 26 weeks of use and Wharton *et al*.[8] at 36 weeks.

In order to analyze the quality of the articles found, the chosen papers were submitted to the JADAD tool – scale used to validate the methodology of randomized clinical trials using a scoring system, ranging from 1 to 5, in which the grade is directly proportional to the quality of the study. Of the five articles found, all presented maximum grade (5), ratifying the quality of the studies.

Results

Five randomized clinical trials were found, in which the sample groups were located in different locations: United States, Canada, Hungary, Germany, Poland and Slovakia. Chart 2 summarizes the main characteristics of the studies used.

Chart 2. Characteristics and main results of the articles used in the results of this work.

Author and year	Design	Sample and setting	Objectives	Main results
Wharton *et al.*, 2023[8]	Phase 2 double-blind randomized trial	A total of 272 non-diabetic men and women aged between 18 and 75 years old who had a BMI > 27 kg/m² and had a stable weight for three months, associated with at least one of the following conditions: hypertension, dyslipidemia, cardiovascular disease or obstructive sleep apnea, were selected. The average age of the participants was 54.2 years, 59% were female and 91% were white.	To analyze the effects of Orforglipron in the treatment of obesity.	The use of Orforglipron resulted in a considerable reduction in weight, ranging from -7 kg to -13 kg in relation to the weight at the beginning of the study. There was a decrease in BMI, ranging from -2.5 to 4.6 in the last week of use. The placebo-corrected change from baseline in abdominal circumference also ranged from -5.6 cm to -9.6 cm. Systolic blood pressure decreased by -10.5 mmHg, while diastolic blood pressure showed no significant changes. The mean percentage of participants with adverse effects was 88% in those receiving orforglipron and 76% in those receiving placebo.
Frias JP *et al.*, 2023[9]	Double-blind randomized clinical trial	226 men and 157 women aged 18 years and over, diagnosed with type 2 diabetes mellitus, who had glycated hemoglobin between 7 and 10.5% and a stable BMI of 23 kg/m2 or more.	To evaluate the efficacy and safety of Orforglipron compared to placebo and Dulaglutide in patients with type 2 diabetes.	The mean change in body weight after 26 weeks was -10.1 kg (7.9 kg placebo-adjusted) with Orforglipron, while the change was -2.2 kg with placebo and -3.9 kg with dulaglutide. The incidence of adverse events with Orforglipron treatment ranged from 61.8 to 88.9%, compared with 56% of adverse events among patients treated with Dulaglutide and 61.8% with placebo.
Pratt E. *et al.*, 2023[10]	Phase 1a, double-blind, placebo-controlled, randomized clinical trial.	Ninety-two healthy adults aged 18 to 65 years with HbA1c <6.5% and BMI between 20 and 40 kg/m² were selected. Participants were subdivided into 2 groups. Group "A" evaluated single ascending doses, while group "B" evaluated multiple ascending doses. Doses ranged from 2mg to 24mg. Group A had 32 participants, mean age of 43.4 years, 59% men and 41% women, mean weight of 84kg and mean BMI of 28.8 kg/m². Group "B" had 60 participants, mean age of 42.5 years, 73% men and 27% women, mean weight of 84kg and mean BMI of 28.5 kg/m². At the end, 83 participants took part in the complete study.	To evaluate the efficacy and safety of Orforglipron administered in single and multiple doses of Orforglipron in healthy patients.	The initial half-life of Orforglipron was 24.6 to 35.3 hours, supporting a single-daily dosage. After 28 days, the half-life was 48 to 68 hours. Furthermore, it was observed that the oral glucose tolerance test showed reductions after 2 hours of administration, which ranged from -27 to -79.3 mg/dL, with no relation to doses. The reduction in glucose levels was maintained after 28 days, ranging from -51 to -63.6 mg/dL. Weight loss in 28 days was 4.8 to 5.4 kg with doses equal to or greater than 6 mg. All patients presented weight loss, from -1.1 kg to 9.2 kg in 28 days, while the placebo group presented a final mean weight loss of 2.4 kg (P<0.05). Heart rate increased by 5-13 bpm/min in all groups receiving Orforglipron from 28 days of use. There were no changes in the patients' systolic and diastolic blood pressures.

Pratt E *et al.*, 2023[11]	Phase 1b, double-blind, placebo-controlled, randomized clinical trial	Sixty-nine men and women aged 18 to 70 years who had been diagnosed with type 2 diabetes mellitus for at least 6 months were selected. Inclusion criteria were an HbA1c between 7% and 10.5%, a BMI between 18.5 and 45 kg/m2, and a stable body weight for at least three months. Exclusion criteria were individuals with a history of hospitalization for ketoacidosis or hyperosmolar state for up to 6 months prior to the study, severe or progressive diabetic retinopathy, specific cardiovascular events, or allergies to the test compound.	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of Orforglipron in patients with type 2 diabetes mellitus.	There was a significant reduction in body weight among individuals who used Orforglipron, except at the 21mg dose. Weight loss was approximately -4 to -6 kg with the medication, in contrast to the -0.75 kg lost by the placebo group. Among participants using Orforglipron, 76.5% reported adverse effects related to treatment, with gastrointestinal symptoms being the most common, such as nausea, vomiting and decreased appetite. The incidence of gastrointestinal effects is more related to the 45mg dose.
Ma X *et al.*, 2024 [7]	Randomized study	Study "A" had a sample group of 12 male and female participants aged between 18 and 65 years, mostly white (66.7%), BMI of 20 to 40 kg/m2 and glycated hemoglobin below 6.5%. Study "B" had 34 individuals, both male and female, aged between 21 and 70 years, all Asian, BMI between 18.5 and 35 kg/m2 and weight > 45 kg. Study "B" excluded individuals with hemoglobin levels below the level considered non-anemic, while both studies excluded individuals with cardiovascular, renal, respiratory, endocrine, hematologic, gastrointestinal and neurological diseases.	To investigate the effect of fasting state and postprandial state on the pharmacokinetics, safety and tolerability of Orforglipron	In study A, with a single 3 mg dose of Orforglipron, the concentration-time curve (CCT) and maximum observed concentration (Cmax) were 23.7% and 23.2% lower, respectively, in the group administered the dose after a meal, compared to the fasting group. In study B, with the 16 mg dose, the CCT and Cmax were 17.6% and 20.9% lower in the fed group. In both studies, the half-life values were similar in both the fasting and fed groups, being in study A 29.5 and 27.9 hours, respectively, while in study B the half-life values were 26 hours for the fasting group and 24.6 hours for the fed group. Regarding adverse effects, in study A, two participants (16.7%) reported side effects of nausea during administration in the fasting state, while one participant (8.3%) reported abdominal pain, headache, sneezing and vomiting. Overall, in study A, two participants reported adverse effects, one of which was vomiting. In study B, 64.3% of participants reported at least one adverse effect in the fasting state, while 44.4% reported it in the fed state. The most common effects in study B were nausea, headache, and abdominal distension. One participant (3.6%) discontinued the study due to vomiting in the fasting state.

All articles were published in 2023 and 2024. The randomized studies, in their entirety, presented 5 points in the JADAD scale. Chart 3 shows the analysis of the articles.

Chart 3. Analysis of the quality of randomized clinical trials used in the discussion of this article, according to the JADAD Scale.

Questions	Score				
	Wharton *et al.* 2023	**Frias JP *et al.*2023**	**Pratt E *et al.*2023**	**Pratt E *et al.*2023**	**Xiaosu Ma *et al.* 2024**
1. Was the study described as randomized?	1	1	1	1	1
2. Is the described randomization is appropriate?	1	1	1	1	1
3. Were there comparisons and results?	1	1	1	1	1
4. Are the described comparisons and results appropriate?	1	1	1	1	1
5. Were the losses and exclusions described?	1	1	1	1	1
Total	5	5	5	5	5

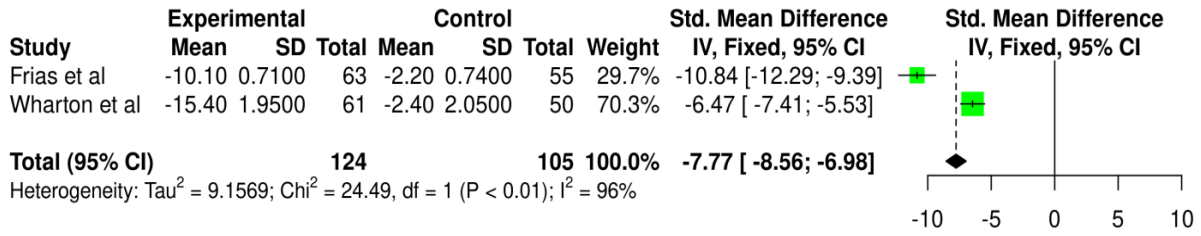
In relation to the analyzed population, there were 861 individuals in the five analyzed studies, being composed of 58.3% men and 41.7% women, aged between 18 and 75 years and BMI between 18.5 and 45 kg/m^2. Two studies associated body weight gain with type 2 diabetes mellitus, and participants with this disease, included in the trials, presented glycated hemoglobin (Hba1c) between 7 and 10.5%[9,11]. All studies used as exclusion criteria other comorbidities besides diabetes[7-11].

Orforglipron was used in different dosages in the five tests[7-11], ranging from 2, 3, 9, 12, 15, 16, 21, 24, 27, 32, 36 and 45 mg, all taken only once a day, both fasting and in the postprandial state. The studies performed different titrations between the doses presented. The study time ranged from 7 weeks to 36 weeks.

All studies used absolute weighing as a tool to define the results of weight loss over the weeks of study[8-11]. One of the studies also used variation of BMI and abdominal circumference[8].

The meta-analysis that compared two randomized studies on the use of Orforglipron at 45mg dose, revealed statistical significance, despite the high heterogeneity I^2=96. The arm of the study that used Orforglipron showed a mean loss of 7.7 kg of body weight during its use (Graph 1).

Graph 1. Forest plot graph referring to the meta-analysis using the fixed effects model methodology between the use of 45mg of orforglipron and placebo.



Discussion

Characterization and mechanism of action of GLP-1 agonists

GLP-1 is a peptide composed of 31 amino acids consisting of an insulin-dependent incretin secreted by the ileum and colon L cells in response to carbohydrate intake. Thus, with the increase of serum concentration of GLP-1, this peptide binds to six specific receptors and are rapidly cleaved by the enzyme Dipeptidil Peptid IV (DPP-IV), stimulating the β-pancreatic cells to secrete insulin and reduce the release of glucagon.

In addition, the constant presence of incretin stimulates long-term proliferation and hypertrophy of pancreatic beta cells; promotes the gene expression of the glucose cotransporter GLUT-2- increasing the peripheral and hepatic uptake of this monosaccharide to the glycolytic pathway and reducing its serum concentrations; stimulates the secretion of somatostatin – inhibitory hormone of the digestive tract, with consequent decrease in the time of gastric emptying, and decreases the apoptosis of β-pancreatic cells[14]. As a result of different mechanisms, insulin secreted in higher concentration promotes the expression of leptin mRNA, a hormone responsible for hypothalamic modulation of satiety, and regulates plasma glucose levels. In this sense, GLP-1 agonist drugs appeared in an attempt to mimic this mechanism of action and promote weight loss and glycemic control in patients with obesity and DM2[13,14].

Characteristics of GLP-1 agonist molecules

Currently, the most used drugs of this class are Liraglutide (Saxenda®) and Semaglutida (Ozempic®), with weekly subcutaneous doses. Liraglutide is a drug with 97% amino acid similarity to endogenous GLP-1, differing only by the substitution of lysine for arginine at position 34 and by presenting a palmitate conjugated to a lysine at position 26 through a glutamate site. Semaglutide, in addition to these two chemical alterations, also presents the substitution of an alanine amino acid by an α-aminoisobutyric acid at position 8, resulting in a 94% homology with the human GLP-1

peptide. These structural changes decrease the susceptibility to DPP-IV, besides that the fatty acid coupled to Semaglutida inhibits the albumin binding, creating a long-acting analogue of GLP-1 – conjuncture that justifies the more intense effect of Semaglutida compared to Liraglutide. The most common adverse effect is nausea, but with low prevalence in patients. However, since these are peptide medications with high homology to endogenous incretins, the cost of production is high, which makes treatment expensive and inaccessible for a significant portion of the population[13,14].

Etiology of obesity and available treatments

Obesity is a multifactorial disease. Among the exogenous etiologies, environmental factors are highlighted, such as high-calorie diet associated with different levels of sedentary as well as genetic polymorphisms that predispose and influence the individual's ability to optimize the oxidation of fats in the body and chronic use of some medications, such as typical antipsychotics or first generation, such as Chlorpromazine, Haloperidol and Levomepromazina[1].

Endogenous etiologies have little influence on the overall scenario of obesity. This includes endocrine diseases such as hypothyroidism, Cushing's syndrome, craniopharyngioma and unsatisfactory levels of growth hormone (GH); genetic and chromosomal-based diseases such as the Down syndromes, Prader-Willi, Laurence-Schiller, Bardet-Biedle, Alstrom; and mutations that alter anorexic regulation, such as leptin gene or receptor (hypothalamic satiation hormone) and pro-opiomelanocortina (POMC) – satiety agonist via the alpha-melanocyte-stimulating hormone (α-MSH)[1].

There are currently multiple treatments for obesity, all complementary to lifestyle changes (based on constant physical activity – at least 150 minutes per week according to WHO - and hypocaloric or normocallogenic eating habits)[1]. In the pharmacological field, the first approved substances were phentermine, diethylpropion, fendrimetazine and benzfetamina hydrochloride, compounds that influence the noradrenergic and dopaminergic neurotransmission and result in a decrease of appetite by modulation of the Central Nervous System[12]. Nevertheless, the aforementioned substances have low tolerability and significant side effects and therefore do not fit into the ideal scenario of an anti-obesity medication[3].

It is worth mentioning that, for an anti-obesity drug to be viable, the substance must demonstrate effects in reducing body weight – generally at least 5% of initial weight in the first three months of treatment; have few side effects and, when they are present, tolerable and/or transient; not present high degrees of dependence; demonstrate efficacy and long-term safety; have known and predictable mechanism of action and, ideally, affordable cost so that treatment does not become expensive[3].

When the pharmacological treatment is insufficient and/or ineffective, surgical treatment may be considered. Bariatric surgery has clear indications and should be a consensus in the multidisciplinary assessments of the team that accompanies the patient. The surgery is indicated for patients aged between 18 and 65 years, with BMI > 40 kg/m^2 without comorbidities or BMI > 35 kg/m^2 with one or more comorbidities related to overweight, and the surgically induced weight loss will present benefits in the improvement or resolution of these comorbidities. Furthermore, proof of failure of anti-obesity treatments for at least two years is required (dietary control, regular physical activity, psychotherapy and pharmacological treatments)[1].

The treatment options for weight management currently available are GLP-1 receptor agonists, Liraglutide (0.3 mg daily) and Semaglutide (2.4 mg weekly), which have as main obstacles the low adherence to the injectable formulation and the consequent discontinuity of long-term treatment. Although the oral formulation of Semaglutide has been approved, its efficacy is demonstrably lower than that of the injectable medicament[4], and its tolerability and effect are conditioned to fasting intake, 30 minutes before the first meal, with a maximum of 120 mL of water to aid in swallowing the medication[5].

Use of Orforglipron in the treatment of obesity

Orforglipron (LY3502970) is a new GLP-1 agonist and one of the first chemically synthesized non-peptide drugs that present good oral bioavailability, without the need for incorporation of complex chemical agents to increase absorption[10]. Its development has as a proposal a greater adherence to the continuity of therapy, compared to other available GLP-1 receptor agonists, and higher percentage of body weight loss.

Concerning the bioavailability of this drug, a clinical phase 1 article described two randomized trials that aimed to investigate the pharmacokinetics and tolerability of Orforglipron after its ingestion, both in fasting and in the postprandial state. In both studies, participants were randomly selected from a group with no restrictions on drug use and another group where the administration is done after 10 hours of fasting. It is concluded that the pharmacokinetics of Orforglipron are decreased when consumed outside fasting, since the maximum concentration was on average 22% lower in the fed state in both studies described, as well as the concentration-time curve is also on average 20.6% lower. However, the article concludes that the pharmacokinetic difference would not cause significant changes in clinical efficacy according to the prandial status[7].

As to the effectiveness of this medication, the results of the other studies under discussion corroborate the maintenance of effects, regardless of the mode of administration. A randomized phase 2 study administered Orforglipron in oral capsule without restriction of meal time or

association with water and food. The study demonstrated that the drug is highly effective in losing body weight, with an absolute and continuous decrease. Weight loss ranged from -7.4 kg to -13 kg compared to the baseline in just 36 weeks, and with a prospect of progression of results with the continuation of treatment, even without fasting or feeding restrictions8. Another multicenter randomized study in patients with mandatory T2DM diagnosed showed an average decrease of body weight of -10.1 kg, compared to the loss of -2.2 kg with the use of placebo[9]. Finally, two randomized trials, in their phases 1a and 1b, which differ in the sample group with healthy participants and participants with type 2 diabetes mellitus, respectively, also showed a significant decline in body weight, corroborating with the other studies supervisible[10,11]. In all studies, the dose-dependent relationship with the effect of weight loss was reported, and it was also highlighted that the use of Orforglipron was associated with lifestyle changes. The meta-analysis comparing the use of 45mg versus placebo revealed statistical significance in favor of the use of Orforglipron for the treatment of obesity.

Orforglipron was compared with other GLP-1 agonists, and the drug was compared to dulaglutide in one of the studies[9]. While the weight reduction with Orforglipron was -10.1 kg in 26 weeks, that of Dulaglutide was only -3.9 kg, showing the superiority in efficacy of Orforglipron. A systematic review, conducted by Hong Li *et al.*[12], corroborates the above results. The review consisted in evaluating the efficacy of GLP-1 receptor agonists for the effect on body weight loss, and it was concluded that Orforglipron was the second most effective, below only CagriSema and above Liraglutide and Semaglutida (the probabilities were: CagriSema: 0.9948; Orforglipron: 0.8159; Semaglutide: 0.8054)[12].

In relation to the reduction of abdominal circumference, only one study shows in its results a considerable decrease of -5.6 to -9.6 cm with respect to the beginning of the use of Orforglipron, which infers effectiveness in weight loss. This same work also reports a drop in BMI from -2.5 to -4.6 kg/m[28].

As for adverse effects, all studies cited that gastrointestinal symptoms are the most present during the use of Orforglipron. Among these, nausea, vomiting, constipation and dyspepsia are the most common. Symptoms ranged from mild to moderate and none of the studies reported serious side effects, such as cardiovascular events, altered liver enzymes, severe hypoglycemia or acute pancreatitis[7-11]. A randomized study, in its phases 1a and 1b, reported increased amylase and lipase, which normalized after some days[10, 11]. The studies agree that the side effects of Orforglipron are equivalent to the effects of other GLP-1 receptor agonists.

In a study comparing safety and tolerability in fasting and postprandial states, a higher rate of diverse side effects was reported in participants who took Orforglipron during fasting in both

studies described. Postprandial intake showed fewer adverse events, but a higher incidence of common gastrointestinal symptoms[7].

Regarding the optimal dosage for weight loss, all studies have used different titration strategies of several dosages of Orforglipron in order to find the safest and most effective dose, ranging from 2mg to 45mg. As the loss of body weight increased with increasing dose, being dose-dependent effect, the incidence of adverse events was also higher in the highest dosages in all studies that made the comparation[8,10,11]. However, the highest index of gastrointestinal symptoms in the dose of 45mg is mainly related to how the dosages were titrated, until reaching the highest. It was concluded that side effects were greater when treatment is started with the dose of 3 mg, instead of 2 mg, even reaching the same target dosage of 45 mg. The same effect occurs when the increase in the dose happens every 2 weeks, leading to a greater amount of gastrointestinal symptoms than when the dose is increased after a longer interval of 3 in 3 weeks[8]. Given the findings, it is suggested to start treatment with Orforglipron with lower initial doses of 2 mg and perform the progression as gradually as possible, preferably every 3 weeks, mainly in patients with lower tolerability to other drugs or with previous gastrointestinal symptoms.

The limitations of the results obtained, according to the described works, concern the restrictions of the studied population. Most studies had participants with leucoderma and male sex, besides establishing as exclusion criteria individuals with other comorbidities beyond T2D. There are no studies on the use of Orforglipron in individuals with greater severity, such as those with heart, liver or kidney failure, as well as endocrine, hematological or pulmonary disorders. Thus, the safety of association of other comorbidities besides T2DM with Orforglipron is not yet known. All the randomized trials analyzed were sponsored by the same pharmaceutical company.

Conclusion

Orforglipron is effective in body weight loss, being one of the most effective among the agonists of the GLP-1 receptor, besides standing out for the easy dosage. It has side effects, mainly gastrointestinal, equivalent to other agonists, being safe to be used. There are no studies with a larger sample group, capable of evaluating its safety and efficacy in individuals who present other comorbidities, Type 2 diabetes mellitus. The conduct of new studies by groups not sponsored by the pharmaceutical industry to corroborate the results observed in this systematic review will be of fundamental importance.

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