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EFFECTIVENESS OF APPETITE SUPPRESSANTS IN THE TREATMENT OF OBESITY: A SYSTEMATIC REVIEW

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ABSTRACT
Obesity is a multifactorial condition that requires integrated treatments, including anorectic drugs as a complement to lifestyle changes, which act on the central nervous and endocrine systems, promoting satiety and weight loss. However, inappropriate use can cause adverse effects and dependence, highlighting the need for the present study. This study aimed to analyze the effects and adverse reactions of the main anorectic drugs. Specifically, we sought to characterize their classes and describe the side effects associated with their isolated or combined use. A systematic review was carried out covering 3,905 articles identified in databases such as PubMed, SciELO, Cochrane Library, and other platforms. After applying criteria based on the PICOS model, 625 studies were considered eligible, and five observational studies, published between 2014 and 2024, were analyzed in detail. Methodological quality was assessed by the Newcastle-Ottawa scale. The five studies analyzed approximately 691 thousand participants from different countries. Liraglutide was the most effective in weight loss, with an average of -7.7 kg, while phentermine-topiramate stood out in weight reduction, with more than 40% of cases recording a loss of more than 5% of body weight. However, adverse effects such as nausea, insomnia, and cardiovascular risks were reported. The efficacy of the drugs varies between classes, with liraglutide and phentermine-topiramate being the most promising. The combination of pharmacological interventions with lifestyle changes proved to be more effective and safe, reinforcing the importance of medical supervision. Anorectics are valuable tools in the management of obesity, as long as they are used under medical supervision and associated with healthy habits. Personalized strategies and future studies are essential to ensure long-term safety and efficacy.

Keywords: Obesity. Treatment. Medications. Adverse Effects. Weight loss.

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INTRODUCTION

The origin of excess weight is multifactorial, involving modifiable factors, such as physical inactivity, poor sleep, and excessive calorie consumption, as well as non-modifiable factors like genetic predisposition and intrinsic metabolic dysregulation. Thus, it is a global health issue that requires a multidisciplinary treatment approach, which initially focuses on non-pharmacological methods to reduce cardiometabolic risk. On the other hand, in pharmacological treatment, anorexigenic medications act as secondary interventions, provided that individuals follow the appropriate steps for weight loss and are under medical supervision (Barbosa et al., 2023; Costa et al., 2022).

In this context, appetite-regulating drugs have been widely used as systemic anorexigenic mechanisms, acting simultaneously on the central nervous system, gastrointestinal system, and endocrine system. This complex pharmacological interaction plays a key role in inhibiting peptides and neuropeptides that modulate food intake. Therefore, these appetite-suppressing drugs are also used to treat obesity. In this regard, it is crucial to understand the impact of these anorexigenic medications on energy homeostasis and their systemic effects (Rubnic et al., 2024).

Appetite modulators are mostly synthetic drugs derived from amphetamines, which act on various sites, particularly in the hypothalamic centers of appetite. They function as satiety signals, controlling the endocrine release of bile and pancreatic lipase, which inhibit fat absorption and regulate glucose levels, acting similarly to GLP-1 in the digestive system. Therefore, due to the nutritional deficit resulting from these processes, the body starts using energy reserves, leading to weight loss (Dutra et al., 2015; Carvalho et al., 2021).

From this perspective, pharmacology categorizes these drugs into several relevant classes: catecholaminergic, serotonergic, thermogenic, and fat absorption inhibitors. According to the annual report from the United Nations (UN), daily consumption of these drugs is high in Brazil, with an application of 12.5 doses/day. According to the National Health Surveillance Agency (ANVISA), the most commonly used are lofepramine, mazindol, femproporex, and sibutramine (Neto et al., 2021; Carvalho et al., 2021).

The Federal Council of Medicine (CFM) approves the production, commercialization, and consumption of anorexigenic drugs for obesity treatment, however, only under medical prescription, as these drugs are essential for pharmacological therapy of the disease. However, appetite suppressants have been used abusively and indiscriminately by

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individuals seeking rapid weight loss. In this scenario, it is evident that indiscriminate use and self-medication can lead to physical dependence and cause side effects both in mental and behavioral functions (Carvalho et al., 2021; Souza et al., 2022).

Furthermore, the side effects of appetite-depressing drugs present a significant obstacle to bodily homeostasis. Among the major physiological implications are: systemic arterial hypertension, tachycardia, dysphoria, arrhythmia, and headaches, as well as psychotropic adverse effects, such as seizures, anxiety, and depression. Additionally, these drugs present an unfavorable long-term risk-benefit ratio for the user, with their effectiveness being questioned. Continuous use of these drugs could lead to the development of chronic pathologies or dysfunctions (Costa et al., 2022).

Thus, considering the pharmacological characterization of appetite modulators, it is relevant to consider the risks involved in the abusive use of these drugs, as their impact on the user's health causes both short- and long-term adverse effects, as well as the potential for dependence. In this light, a more thorough discussion of the topic will provide a better understanding of the issues associated with indiscriminate use.

METHODOLOGY

BIBLIOGRAPHIC SEARCH

For the preparation of this work, a search was conducted in electronic databases (PUBMED, SciELO, Cochrane Library, CAPES Periodicals, and the Regional Portal of the Virtual Health Library - BVS). The search strategy used in the review process was based on consultation with the Medical Subject Headings (MeSH) and Descriptors of Health Sciences (DeCS).

In this context, the following MeSH descriptors were used for the search in PUBMED, SciELO, and Cochrane Library: "Obesity" OR "Obesidad" AND "Weight Loss" OR "Emagrecimento" OR "Perda de Massa Corporal" OR "Weight Loss" AND "Antiobesity Drug" OR "Anti Obesity Agents". Regarding DeCS descriptors, "Antiobesity Drugs" "Weight Loss" AND "Obesity" were used.

For the selection of scientific articles, eligibility criteria were established based on the PICOS model, with the guiding question: "What are the effects of the main anorexigenic medications in reducing obesity?" (Table 1). Using this search procedure, 3,905 potentially eligible publications were identified without applying any filters.

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Table 1: Demonstration of the PICOS strategy for the development of the guiding question and theme.

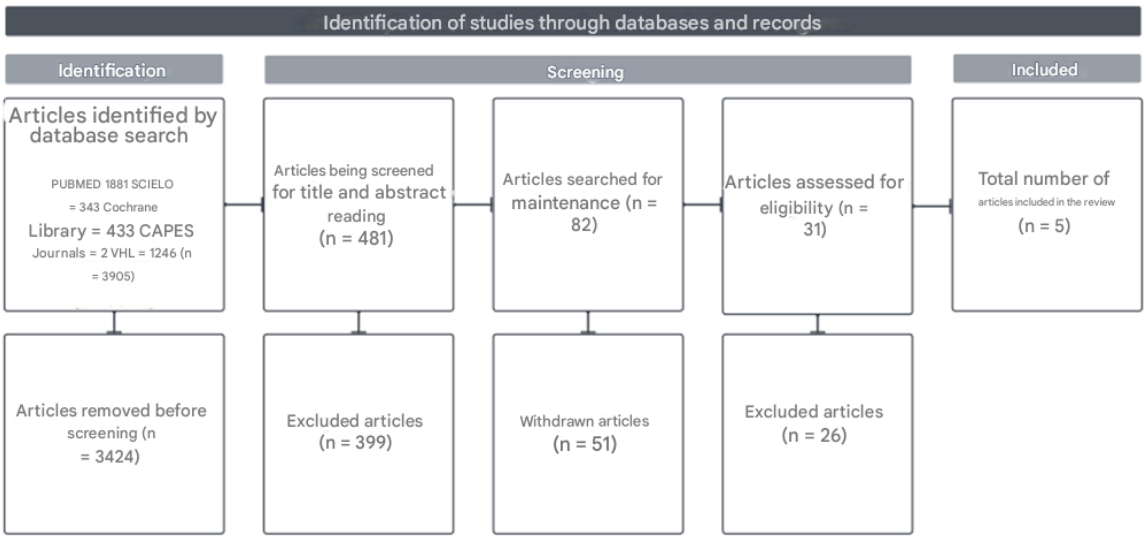
P	Adults diagnosed with obesity and overweight (BMI ≥ 25)
I	Appetite-suppressing medications
C	Among the medications analyzed
O	Effectiveness in weight loss, improvement in quality of life, and possible side effects
S	Observational studies (cohort and case-control)

Legend: P = problem, I = intervention, C = comparison, O = outcome, S = studies. Source: Prepared by the authors.

In this study, only observational methodology works were included, such as cohort and case-control studies. Eligibility criteria included articles published between 2014 and 2024 and adults who were obese or overweight (BMI > 25). Studies that did not meet these criteria include: articles not available in full text, duplicated studies, literature reviews, and studies with children and adolescents as the primary audience.

After applying the filters, 625 articles were considered eligible for analysis, distributed as follows: PUBMED (54), SciELO (217), Cochrane Library (155), CAPES Periodicals (2), and BVS (197). These studies were exported to the Rayyan platform for independent abstract analysis and selection of articles meeting the inclusion criteria for full-text reading. In case of disagreement between researchers, discrepancies were resolved by consensus. Finally, the results were organized and presented in the PRISMA flow diagram (Figure).

Figure 1: PRISMA flowchart.



AUTHORS

To extract the data, a Word spreadsheet was used to organize the characteristics of the studies, such as authors, country, year of publication, and methodological information (type of study, sample size, medications used, and general outcome).

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QUALITATIVE EVALUATION

The Newcastle-Ottawa scale (WELLS et al., 2000) uses a star system to assess the risk of bias in the studies analyzed. This tool assesses three domains: selection of study groups, with a maximum of 5 stars; comparability of groups, with a maximum of 2 stars; and description of results, with a maximum of 3 stars. The higher the number of stars, the lower the risk of bias and, therefore, the better the methodological quality of the study.

This assessment process was carried out by two researchers independently, to minimize the risk of bias in the analysis itself. Disagreements were resolved by consensus among the evaluators. A table was created to fill in the characteristics of the studies and generate graphs and summaries of the risk of bias. Microsoft Excel 2024 was used to organize the data into tables.

APPLICATION OF THE NEWCASTLE-OTTAWA SCALE

The studies included in the systematic review were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS), a tool widely used in cohort studies. The NOS performs a structured analysis based on three main domains: Selection, Comparability, and Outcome, assigning scores according to compliance with specific criteria.

In the Selection domain, the following were analyzed: the representativeness of the cohort, the selection of the control group, the confirmation of exposure, and the clear definition of the outcome, with a maximum score of 4 stars. In the Comparability domain, the adjustment for main factors and other relevant factors was assessed, with up to 2 stars possible. Finally, the Outcome domain considered the assessment of the outcome, adequate follow-up, and losses during follow-up, with a maximum score of 3 stars. Thus, the application of the Newcastle-Ottawa Scale ensures a systematic and objective assessment of the methodological quality of the included studies.

RESULTS

This study identified five relevant studies, conducted in different countries, reflecting significant geographic and methodological diversity. The studies were conducted in Canada, the United States, England, and the United Kingdom, covering diverse populations and distinct contexts in obesity management. Most used retrospective and prospective observational designs, with sample sizes ranging from 43 to more than 624

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thousand participants, totaling approximately 691 thousand individuals analyzed. This distribution increases the relevance of the findings, allowing us to evaluate the efficacy and safety of different pharmacological interventions, as shown in the table 2.

Table 2. Distribution of the selected articles for analysis.

N = 5	Authors/ Year	Country of Origin	Type of Study/ N	Medication	Outcome
1	Gorgojo-Martinéz et al., 2019	Canada	Retrospective and observational cohort	N = 500	Orlistat 120 mg 3x/day and Liraglutide (up to 3 mg/day)
2	Pendse et al., 2021	United States	Retrospective cohort	N = 43	Metformin associated with Liraglutide/ compared to Fentermine-Topiramate use.
3	Calderón et al., 2022	England	Retrospective cohort	N = 304	Fentermine-Topiramate; Liraglutide; Bupropion/Naltrexone; Lorcaserine
4	Douglas et al., 2014	United Kingdom	Longitudinal observational cohort	N = 624,196	Orlistat, Sibutramine
5	Grabarczyk et al., 2018	United States	A multicenter observational cohort study	N = 66,035	Orlistat, Lorcaserine, Fentermine, Fentermine-Topiramate

Legend:
N = Sample size
MOVE! = Lifestyle change intervention
DM 2 = Type 2 Diabetes Mellitus
CAD = Coronary Artery Disease
CVD = Cardiovascular Disease
FPG = Fasting Plasma Glucose
SBP = Systolic Blood Pressure
LDL-C = Low-Density Lipoprotein Cholesterol
ALT = Alanine Aminotransferase
Source: Authors

The studies included in this review assessed a wide range of medications used in obesity treatment, classified based on their pharmacological classes and mechanisms of action. Each drug has unique characteristics that influence its efficacy and safety in weight management. Table 3 presents these details, highlighting the studied medications, the physiological mechanisms involved in weight reduction, their pharmacological classes, and the studies that investigated them.

These interventions include lipase inhibitors, incretin mimetics, appetite moderators, amphetamines, and hypoglycemics, with mechanisms ranging from the reduction of nutrient absorption to the modulation of neurotransmitters and hormones that regulate appetite.

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Table 3. Explanatory chart of the main medications used, based on the articles selected for the review.

Studied Medication	Study(ies) Applied	Pharmacological Class	Physiological Mechanism of Anorexigenic Effect
Orlistat/Orlistatine	Gorgojo-Martinéz et al., 2019Douglas et al., 2014	Appetite moderator - Pancreatic lipase inhibitor	Works by decreasing the digestion of ingested lipids by permanently binding to the active site of lipase in the gastrointestinal lumen. It is a long-lasting drug (Silva; Junior, 2022).
Efpeglenatide	Pratley et al., 2019	Hypoglycemic of the incretin mimetics class	GLP-1 receptor agonist (a hormone produced by enteroendocrine L cells in the ileum and colon), delays gastric emptying. It produces antidiabetic effects by improving insulin sensitivity. Crosses the blood-brain barrier to act on the hypothalamic satiety center (Utta; Pessoa, 2021).
Sibutramine	Douglas et al., 2014	Appetite moderator - Sympathomimetics class	Initially an antidepressant, it works by inhibiting the reuptake of serotonin and norepinephrine. It acts on serotonergic 5-HT receptors, adrenergic (β), dopaminergic, and histaminic (H1) receptors. It causes appetite suppression (Utta; Pessoa, 2021) (Silva; Junior, 2022).
Lorcaserin	Grabarczyk et al., 2018Calderón et al., 2022	Appetite moderator - Anorexigens class	Inhibition of serotonin reuptake; binds to the 5-HT2C receptor, causing satiety effects and suppressing appetite (Utta; Pessoa, 2021).
Phentermine	Grabarczyk et al., 2018	Appetite moderator - Amphetamine class	Anorexigenic effects, acts on sympathomimetic amines (Sala; Moraes; Ferreira, 2023).
Phentermine - Topiramate	Grabarczyk et al., 2018Pendse et al., 2021	Phentermine - Amphetamine classTopiramate - Anticonvulsant	Topiramate is an anticonvulsant that inhibits the dopaminergic pathway, blocking glutamate, GABA, and isoenzymes II and IV of carbonic anhydrase. It produces appetite suppression side effects (Sala; Moraes; Ferreira, 2023).
Metformin	Pendse et al., 2021	Hypoglycemic of the biguanides class	Reduces gluconeogenesis, decreasing glucose absorption in the gastrointestinal tract, leading to weight loss effects (Ferreira; Campos, 2014).
Empagliflozin	Pendse et al., 2021	Hypoglycemic of the SGLT-2 inhibitors class	Inhibits glucose transport in the proximal tubule of the nephron, stimulating glucosuria, restoring insulin sensitivity, and causing weight loss effects (Calado; Nunes, 2015).
Liraglutide	Calderón et al., 2022Pendse et al., 2021Gorgojo-Martinéz et al., 2019	Hypoglycemic of the incretin mimetics class	Acts on pancreatic beta cells to increase insulin secretion, providing an agonist effect on GLP-1 receptors (hormone produced by ileal cells). Its mechanism favors pro-opiomelanocortin (POMC) in the hypothalamus, inhibiting NPY (Neuropeptide Y) and AgRP, increasing satiety and reducing hunger (Utta; Pessoa, 2021).

Source: Prepared by the authors.

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The studies selected for the systematic review underwent an assessment of methodological quality using the Newcastle-Ottawa Scale (NOS) tool. In the selection domain, two studies (Calderón et al., 2022, and Douglas et al., 2014) achieved the maximum score of 4/4, while the others reached 3/4, reflecting a solid methodological design in most of the studies - Table 4.

Table 4. Presentation of results from the methodological quality analysis for each included study using the Newcastle-Ottawa Scale (NOS) based on the Selection Domain.

Cohort Study (n=5)	Author and Year	Selection	Total 0-4
	Representativeness of the cohort	Control group selection	Exposure confirmation
1	Gorgojo-Martinéz et al., 2019	★	★
2	Pendse et al., 2021	★	★
3	Calderón et al., 2022	★	★
4	Douglas et al., 2014	★	★
5	Grabarczyk et al., 2018	★	★

Source: Prepared by the authors.

Table 5. Presentation of results from the methodological quality analysis for each included study using the Newcastle-Ottawa Scale (NOS) based on the Comparability Domain.

Cohort Study (n=5)	Author and Year	Comparability	Total 0-2
	Adjustment for main factors	Adjustment for other relevant factors	
1	Gorgojo-Martinéz et al., 2019	★	★
2	Pendse et al., 2021	★	
3	Calderón et al., 2022	★	
4	Douglas et al., 2014	★	
5	Grabarczyk et al., 2018	★	★

Source: Prepared by the authors.

Table 6. Presentation of results from the methodological quality analysis for each included study using the Newcastle-Ottawa Scale (NOS) based on the Outcome Domain.

Cohort Study (n=5)	Study and Year	Outcome	Total 0-3
	Outcome assessment	Adequate follow-up	Losses to follow-up
1	Gorgojo-Martinéz et al., 2019	★	★
2	Pendse et al., 2021	★	★
3	Calderón et al., 2022	★	
4	Douglas et al., 2014	★	★
5	Grabarczyk et al., 2018	★	★

Source: Prepared by the authors.

Table 7. Evaluation of Methodological Quality of Cohort Studies Using the Newcastle-Ottawa Scale (NOS).

Cohort Study (n=5)	Study and Year	NOS Score (0-9)	Study Quality
1	Gorgojo-Martinéz et al., 2019	8/9	High Quality
2	Pendse et al., 2021	6/9	Moderate Quality
3	Calderón et al., 2022	6/9	Moderate Quality
4	Douglas et al., 2014	7/9	High Quality
5	Grabarczyk et al., 2018	7/9	High Quality

Source: Prepared by the authors.

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Finally, in general, the studies demonstrated good methodological quality, with some studies that obtained high scores in all domains standing out. However, the analysis revealed areas for improvement, particularly in the control of secondary confounding factors and in the consistency of sample follow-up, aspects that should be considered in future investigations.

DISCUSSION

According to the Brazilian Medical Association (2010), obesity is a complex and multifactorial health condition, requiring integrated approaches for its management. Therefore, it is crucial to implement actions that encourage changes in the lifestyle of individuals affected by this condition, enabling effective treatment and improvements in quality of life (Utta and Pessoa, 2021).

In this context, pharmacological treatment stands out as a therapeutic strategy of great importance for the management of obesity. This approach is especially indicated in situations in which interventions based exclusively on lifestyle modification, such as dietary changes, increased physical activity and psychological support, prove insufficient to promote significant weight loss. Furthermore, its application is particularly relevant in the presence of associated comorbidities, such as type 2 diabetes, high blood pressure and dyslipidemia, which often worsen the clinical picture and require more comprehensive interventions (Mancini and Halpern, 2002; Utta and Pessoa, 2021).

In relation to the five articles selected in this research, for a better understanding of the pharmacological and physiological effects of the drugs analyzed, it was decided to group each class of drugs in order to correlate the findings and describe the mechanisms of action and their effects on the organism of individuals with some degree of obesity.

ANOREXIGENIC DRUGS

Anorexic drugs are substances or drugs capable of promoting weight reduction by decreasing appetite, acting on the modulation of catecholaminergic and/or serotonergic neurotransmitters (Oliveira, 2021). According to Dias et al. (2021), these drugs play an important role in the management of obesity, a multifactorial and growing condition globally, especially in countries such as Brazil, which has high prevalence rates.

However, Silva et al. (2023) warn that the inappropriate or indiscriminate use of these drugs can lead to significant health risks, including dependence, cardiovascular and

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psychological disorders. Thus, the use of anorectics must be carefully evaluated and integrated into comprehensive therapeutic strategies to ensure efficacy and safety in the management of obesity.

SIBUTRAMINE

Sibutramine, originally belonging to an antidepressant drug class, acts on serotonergic (5-HT), adrenergic (β), dopaminergic and histamine (H1) receptors, promoting inhibition of the reuptake of serotonin and norepinephrine. This mechanism confers anorectic effects, such as appetite suppression and consequently weight loss (Utta and Pessoa, 2021; Silva; Júnior, 2022).

In the study conducted by Douglas et al. (2014) in the United Kingdom, using a cross-sectional cohort based on data from the UK Clinical Practice Research Datalink (CPRD), the effects of sibutramine compared to Orlistat in obese patients were evaluated. The research involved 624,196 participants, divided into groups that received one of the medications or no treatment, with follow-up for three years. The treatment regimen included the alternating use of sibutramine and Orlistat for 30 consecutive days, alternating every three months. Data such as body mass index (BMI) and the presence and/or evolution of comorbidities were analyzed. The results showed that patients treated with sibutramine had an average weight loss of 1.28 kg/month in the first four months, followed by a gradual weight gain of 0.27 kg/month between five and 24 months and 0.08 kg/month between 25 and 36 months. Patients with cardiovascular disease showed a smaller initial weight loss (1.12 kg/month), while those with diabetes showed an even more limited reduction (0.94 kg/month). The average initial weight was 101 kg (SD = 21 kg), remaining consistent across the subgroups evaluated, indicating the efficacy of the drug in reducing body weight. Although sibutramine helps with weight loss, there are concerns about its cardiovascular side effects, such as increased heart rate and blood pressure. These risks have led to restrictions or withdrawal of the drug in some regions, reinforcing the need for medical monitoring during treatment (Douglas et al., 2014). 4.3 ORLISTATE

In the results analyzed, Orlistat, widely recognized for its action as an inhibitor of gastrointestinal lipase, demonstrated moderate efficacy in reducing body weight, with better results observed in longer-term treatments.ão. Grabarczyk et al. (2018) demonstrated significant weight loss over a 36-week period. However, it should be understood that orlistat, by inhibiting the absorption of fats in the gastrointestinal tract, is associated with

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predominantly gastrointestinal adverse effects, such as fatty stools and fecal urgency, in addition to reduced absorption of fat-soluble vitamins (Silva; Junior, 2022).

In comparative studies, its efficacy was shown to be lower than that of other therapeutic agents. Gorgojo-Martinéz et al. (2019) reported that liraglutide was more effective, with a weight reduction of -7.7 kg, in contrast to -3.3 kg achieved with Orlistat. A similar scenario was observed in the studies by Galati (2024), liraglutide was more effective in weight loss (approximately 6% compared to placebo), with additional benefits in controlling cardiovascular comorbidities.

Furthermore, Douglas et al. (2014) observed that, although Sibutramine outperforms Orlistat in monthly weight loss (-1.28 kg/month versus -0.94 kg/month), Orlistat was more widely used in patients with relevant comorbidities, such as type 2 diabetes mellitus and cardiovascular diseases. On the other hand, comparative studies indicate that, while Orlistat provides moderate and sustained weight loss, Sibutramine offers faster results, but with a higher risk of adverse events, reinforcing the importance of a choice based on the patient's clinical profile and specialized monitoring (Silva; Junior, 2022; Halpern et al., 2000).

In addition, risk factors such as dyslipidemia and Type 2 Diabetes Mellitus (T2DM) were presented as factors that postpone the weight loss results recommended by the pharmacodynamics of Orlistat. This was observed both in the comparative study by Douglas et al. (2014) with Sibutramine, and in the cohort study by Gorgojo-Martinéz et al. (2019), which compared Orlistat with Liraglutide. In these cases, it was identified that patients with more exacerbated baseline indices such as BMI, DM2, dyslipidemia, previous bariatric surgery, mood disorders and sleep apnea had greater weight loss success with Orlistat after controlling such disorders. In this context, the lower efficiency of Orlistat was also observed due to low adherence by users and lower weight loss response in the same period when compared to other anorexiant drugs. Therefore, in cases of options for the treatment of obesity, it is preferable to opt for other drug proposals (Grabarczyk et al., 2018). 4.4 LIRAGLUTIDE Liraglutide is a drug used to control glycemia and produce antidiabetic effects, composing the class of incretin mimetics. It is widely used in the treatment of obesity and has been the subject of numerous studies. It is an agonist of the Acylated Human Glucagon-like peptide 1 (GLP-1) receptor. GLP-1 is a physiological regulator of appetite and calorie intake, and its receptor (GLP-1R) is present in several regions of the brain involved in appetite regulation (ANVISA, 2022). Among such

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moderations, the suppression of the hypothalamic hunger center by the inhibition of NPY and AgRP stands out, increasing the feeling of satiety (Utta and Pessoa, 2021).

In this sense, the study by Gorgojo-Martinéz et al. 2019, carried out in a single center with observational data, compared the clinical efficacy of Orlistat and Liraglutide in obese or overweight patients enrolled in a structured obesity management program, with phases numbered V1, V2 and V3, during which the doses of the medications were adjusted. Both groups followed a hypocaloric Mediterranean diet and a moderate aerobic exercise program, with discontinuation defined as 120 consecutive days without medication use.

Liraglutide demonstrated greater efficacy in weight loss, with mean reductions of -6.4 kg at V2 and -7.7 kg at V3, compared to -3.8 kg and -3.3 kg, respectively, in the Orlistat group. In addition, a greater proportion of patients treated with Liraglutide achieved a ≥ 5% reduction in baseline weight, with adjusted odds ratios indicating up to seven times greater chance of success at V3. Both medications reduced blood glucose and LDL-C, but Liraglutide promoted additional benefits in triglycerides, GGT and waist circumference (in patients with BMI < 35 kg/m²), suggesting better metabolic and cardiovascular outcomes. High costs affected adherence, but discontinuation due to gastrointestinal intolerance was higher with Orlistat (10.8%) than with Liraglutide (1%). The main adverse effects were diarrhea with Orlistat (29%) and nausea (21%) and vomiting (6%) with Liraglutide, which are generally mild and resolutive, thus highlighting the greater efficacy and safety of Liraglutide, considering factors such as tolerability, cost and patient characteristics.

PHENTERMIN AND PHENTERMIN-TOPIRAMATE

Phentermine alone and the combination associated with Topiramate are centrally acting weight loss medications, as they are derived from β-phenethylamine (a chemical structure present in neurotransmitters, such as dopamine, noradrenaline and adrenaline – which are monoamines, present in amphetamines). In this way, β-phenethylamines act by stimulating the release of noradrenaline, increasing both its postsynaptic interaction and its anorectic effects, which are understood by its binding sites in the hypothalamus and brain, with the appetite suppressant impact manifested by satiety and thermogenesis (Mancini; Halpern, 2002). Therefore, Phentermine, as an appetite suppressant of the amphetamine class, and Topiramate, as an anticonvulsant that inhibits the dopaminergic pathway, are effective medications in the treatment of obesity, with regard to their weight loss effects

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(Sala; Moraes; Ferreira, 2023). This effect was observed in the multicenter cohort study by Grabarczyk et al. (2018), whose proposal revealed a higher rate of decrease in body mass of 4.1% in 6 months of use. In this research, to verify the best performance in the loss of at least 5% kg in 6 months, Phentermine-Topiramate demonstrated success in 40.3% of the 233 participants, when compared to other medications, such as Orlistat, Phentermine Isolated and Lorcaserin. It also demonstrated a better effect as opposed to intervention only through lifestyle change (MOVE! program). The latter represented only 26.2% success in the weight loss target applied to the sample of 59,047 (Grabarczyk et al., 2018). From this perspective, in medical prescribing practice, the indication of monotherapy with Phentermine was infrequent when compared to Phentermine associated with Topiramate. This analysis can still be made by comparing the use of hypoglycemic agents whose effect represented -2.5 kg with Metformin compared to -5 kg with Phentermine-Topiramate, during 365 days of continuous prescription (Pendse et al., 2021). 4.6 HYPOGLYCEMIC DRUGS

Hypoglycemic or antidiabetic drugs are drugs used to reduce blood glucose levels, and are especially important in the treatment of type 2 diabetes mellitus. They can be divided into three groups according to their mechanism of action: insulin stimulators (sulfonylureas and metiglinides), insulin sensitizers (biguanides and thiazolidinediones), and alpha-glucosidase inhibitors, which reduce carbohydrate absorption.

According to Domingos et al. (2024), these drugs promote glycemic control, preventing complications such as neuropathy, retinopathy, and cardiovascular diseases, in addition to significantly improving patients' quality of life. When necessary, it is possible to combine different drugs to optimize glycemic control (Marcondes, 2009).

EFPEGLENATIDE

Efpeglenatide, a long-acting GLP-1RA, is administered subcutaneously and has a pharmacokinetic and pharmacodynamic profile that allows flexibility in dosing frequency, ranging from weekly to monthly (Sr, 2016). Regarding this medication, a randomized clinical study conducted by Pratley et al. (2019) sought to understand how this medication acts and its effects occur in obese individuals.

In this scenario, the study by Pratley et al. (2019) used the efpeglenatide dosage regimen that included doses of 4 mg once a week, 6 mg once a week, 6 mg every 2 weeks, 8 mg every 2 weeks, or placebo. Participants were aged between 18 and 65 years,

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in stable health, with fasting glucose levels below 126 mg/dL, and a BMI greater than or equal to 30. Individuals with a BMI between 27 and 30 also participated, provided they had treated or untreated comorbidities such as hypertriglyceridemia, dyslipidemia, hypertension, glucose intolerance, or sleep apnea. Patients with a BMI above 42, medication-induced obesity, type 2 diabetes, or HbA1c above 48 mmol/mol were excluded. In addition, participants were encouraged to adopt a hypocaloric diet and engage in physical activity, although these interventions were not strictly controlled during the study. In this sequence, the same study evaluated 297 participants, of whom 216 completed 20 weeks of treatment with efpeglenatide, showing that all doses resulted in a reduction in body weight, being more significant with 6 mg once a week (-7.2 kg compared to placebo) (Pratley et al., 2019).

In addition, there were significant decreases in waist circumference, fasting blood glucose, HbA1c and lipid profile, except for HDL cholesterol at doses of 4 mg. The dose of 6 mg once a week stood out for its efficacy in reducing systolic blood pressure (-6 mmHg) and in the overall benefit profile, demonstrating that higher doses provide better clinical results compared to lower doses. Adverse events were common (88.1% with efpeglenatide versus 80% with placebo), mainly gastrointestinal, such as nausea, which reduced ziu over time. Ten serious adverse events were reported, including serious cases related to the drug (Pratley et al., 2019).

Studies such as the one conducted by Gerstein et al. (2021) confirm its effectiveness in reducing the risk of adverse cardiovascular events and improving renal parameters in patients with type 2 diabetes and high cardiovascular risk. The analysis revealed that doses of 4 mg and 6 mg significantly reduced the risk of major cardiovascular events compared to placebo (hazard ratio of 0.73; 95% CI, 0.58–0.92; $p = 0.007$) and improved renal outcomes such as albuminuria and glomerular function (hazard ratio of 0.68; 95% CI, 0.57–0.79; $p < 0.001$). These benefits extend to the reduction of blood glucose, body weight and blood pressure, standing out as a safe and effective therapy in the control of obesity and its associated complications (Gerstein et al., 2021).

In addition, as pointed out by Escobar et al. (2023), gastrointestinal adverse events were the most common among participants treated with efpeglenatide, in line with other GLP-1RAs. These events, predominantly mild to moderate, included nausea and diarrhea, but tended to decrease over time. Cardiovascular safety, a critical aspect in the

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management of T2DM, was also evaluated in the AMPLITUDE-O study, which revealed a reduction in the risk of serious cardiovascular events in high-risk patients.

METFORMIN

Biguanides, a subgroup of insulin sensitizers, include metformin hydrochloride, a widely used oral antidiabetic. After administration, the drug is absorbed predominantly in the small intestine, with a bioavailability of 70% to 80% (Goodman and Gilman, 2019). It is subsequently metabolized in the liver and kidneys, with a half-life of approximately three hours (Rang and Dale, 2016). Although the exact molecular targets of metformin are not yet fully understood, its biochemical effects are well established. The drug reduces hepatic glucose production, increases glucose uptake by peripheral tissues, decreases carbohydrate absorption in the intestinal tract, promotes fatty acid oxidation, and reduces plasma LDL and VLDL levels (Rang and Dale, 2016). The efficacy of metformin in weight loss has been investigated in different studies. Pendse et al. (2021) conducted a comparative analysis of the drug with other drugs used for the same purpose, evaluating medical records of obese patients in two settings: a local weight management program and a national database. In the local program, 43 patients participated in the MOVE! intervention, which combined pharmacotherapy (including metformin, liraglutide, and others) with monthly follow-up.

On a national scale, more than 2 million prescriptions were analyzed, focusing on the impacts of metformin. The data revealed an average reduction of -0.034 kg/week in the national analysis. In the local program, metformin was the most used drug, often in combination with other interventions, prescribed to 31 patients. Despite this, the effectiveness of metformin in weight loss was lower than that of drugs such as phentermine-topiramate and liraglutide, which are specifically approved for the treatment of obesity.

Another study, conducted by Seifarth et al. (2013) reinforces the potential of metformin in weight reduction in obese and insulin-resistant patients, even outside the context of diabetes. Over a six-month period, patients treated with the drug showed an average weight loss of 5.8 kg (equivalent to 5.6% of initial body weight), while the untreated control group recorded an average weight gain. These results show that metformin may be especially effective for individuals with greater insulin resistance. Yerevanian and Soukas (2019) elucidate additional mechanisms by which metformin

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contributes to weight loss. In addition to its hypoglycemic action, the drug modulates appetite via the gut-brain axis, alters the intestinal microbiota, and affects energy metabolism. An increase in the secretion of incretins, such as GLP-1, and an improvement in leptin sensitivity were observed, both associated with appetite regulation. Furthermore, the drug promotes changes in the intestinal microbiome, increasing the proportion of beneficial bacteria, such as Akkermansia muciniphila, recognized for their contribution to improving metabolism.

Although studies such as the Diabetes Prevention Program (DPP) have demonstrated sustained weight loss over 10 years in patients with high adherence to treatment, the results are inconsistent in non-diabetic patients. This variability reflects differences in the metabolic profile of the participants, doses administered and methodologies applied in the studies.

EMPAGLIFLOSIN

Empagliflozin, belonging to the group of sodium-glucose cotransporter type 2 (SGLT2) inhibitors, is a drug that acts by inhibiting the transport of glucose into the bloodstream. and glucose in the proximal tubule of the nephron. This mechanism promotes the elimination of glucose in the urine (glycosuria), resulting in a reduction in blood glucose levels. In addition, empagliflozin contributes to the restoration of insulin sensitivity, facilitating glycemic control, and promotes weight loss due to increased glucose excretion, which reduces the amount of calories absorbed by the body (Calado and Nunes, 2015).

In a cohort study conducted by Pense et al. (2021), which evaluated the efficacy of hypoglycemic medications, empagliflozin demonstrated significant benefits in glycemic control and lipid profile. Reductions in fasting blood glucose and HbA1c levels were observed, in addition to decreases in body weight and waist circumference. However, the effects compared to placebo were less expressive than those achieved with other therapies, such as efpeglenatide. In another clinical study, empagliflozin administration in obese adults without type 2 diabetes reduced hepatic gluconeogenesis associated with visceral fat, suggesting a promising mechanism for the prevention of type 2 diabetes in obese individuals (Neeland et al., 2020).

Additionally, preclinical studies have indicated that empagliflozin prevents weight gain, insulin resistance, and hepatic steatosis in diet-induced obesity models, in addition to improving insulin sensitivity and muscle mitochondrial morphology (Radlinger et al., 2023).

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In patients with heart failure, the EMPEROR-Pooled study analysis revealed that the drug reduces hospitalizations and cardiovascular mortality, in addition to slowing the progression of macroalbuminuria and favoring remission to normoalbuminuria or microalbuminuria, regardless of initial albuminuria levels (Ferreira et al., 2022).

Finally, empagliflozin promoted a modest reduction in total and LDL cholesterol levels, with most adverse effects being mild or moderate, such as nausea and gastrointestinal disorders, which are common with drugs that induce glycosuria.

DRUG INTERVENTION AND LIFESTYLE CHANGE

The use of weight-loss medications was more successful when combined with a balanced diet and regular exercise. This fact is crucial, including in the development of cohort studies, such as that of Gorgojo-Martinéz et al. (2019), which defined as a standard the application of a Mediterranean diet with caloric restriction and the practice of moderate-intensity aerobic activities for 30-45 minutes, 3-5 days/week to the research participants.

The lifestyle change incorporated into anti-obesity drugs also proved to be quite successful in the cohort study by Pendse et al. (2021), whose longitudinal monitoring demonstrated weight loss proportional to the time spent exercising by participants.

In this regard, initiatives such as the American program for veterans “MOVE!” were created with the aim of promoting health and preventing diseases, focusing on interventions in nutrition, physical activity and lifestyle changes. According to a multicenter cohort study conducted by Grabarczyk et al. (2018), the comparison of the effectiveness of anorectic drugs showed success in linking pharmacological intervention to non-pharmacological therapies during the 20 weeks of observation. However, exclusively non-pharmacological intervention - such as “MOVE!” - still obtained inferior results to those used together (Grabarczyk et al., 2018).

CONCLUSION

This study highlighted the challenges and advances in the pharmacological treatment of obesity, a complex and multifactorial condition that requires integrated and individualized approaches. Through the analysis of different classes of drugs, including anorectics, hypoglycemic agents and other therapeutic agents, the mechanisms of action, efficacy and risks inherent in the use of these substances were elucidated. This knowledge

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reinforces the importance of specialized medical monitoring in the selection and administration of treatments.

The findings showed that pharmacological interventions, when appropriately indicated and combined with lifestyle changes, such as a balanced diet and regular physical exercise, have the potential to enhance therapeutic benefits and reduce complications. However, the presence of side effects and the dangers associated with the improper or prolonged use of these drugs highlight the importance of a meticulous and multidisciplinary approach.

Therefore, it is concluded that efficient management of obesity must consider biological, behavioral and social factors. Constant investment in studies that investigate new treatments and customized strategies is crucial, aiming to improve global public health.

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