



Major scientific and clinical evidence of pharmacological anti-obesity treatments: a systematic review

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Abstract

Introduction: Obesity is a chronic, complex, and heterogeneous disease that can cause more than 200 comorbidities. In the United States, more than one-third of adults (approximately 35% of men and 40% of women) are obese. It is estimated that by 2030, almost 30% of the adult population in Brazil will be obese. It is known that obesity treatment requires lifestyle changes and that drugs should be administered as a complementary alternative to treatment. **Objective:** Conduct a systematic review to present the main scientific and clinical evidence of anti-obesity pharmacological treatments through anorectic drugs and their associations. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from March to April 2025 in the Web of Science, Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. 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 Conclusion:** A total of 111 articles were found. A total of 30 articles were fully evaluated, and 21 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with high risk of bias and 21 studies that did not meet the GRADE and AMSTAR-2 criteria. Most studies presented homogeneity in their results, with $X^2=78.7\% >50\%$. It was concluded that the scientific findings of randomized studies on the use of anorectic drugs to treat obesity have shown safety and efficiency in the last five years, presenting reasonable weight loss and no significant complications. The combination of naltrexone-bupropion was significantly superior to placebo. Pharmacotherapy for obesity should be conducted according to an adequate assessment of clinical evidence and personalized for each patient, considering the characteristics of each drug and comorbidities associated with obesity. Adults with binge eating disorder and obesity who responded to acute treatment

with lisdexamfetamine (whether or not they received additional cognitive-behavioral therapy) had good maintenance over the subsequent 12 weeks. Maintenance with lisdexamfetamine, relative to placebo, did not provide additional benefit for binge eating, but was associated with significantly better eating disorder psychopathology outcomes and greater weight loss.

Keywords: Anorectic drugs. Anti-obesity drugs. Obesity. Weight loss.

Introduction

Obesity is a chronic, complex, and heterogeneous disease that can cause more than 200 comorbidities. In the USA, more than one-third of adults (approximately 35% of men and 40% of women) are obese [1]. According to the Ministry of Health, obesity affects more than 6.7 million people in Brazil. The number of people with morbid obesity or body mass index (BMI) grade III, above 40 kg/m², reached 863,086 people in 2022. It is estimated that by 2030, almost 30% of the adult population will be obese in Brazil [2].

The rapid increase in obesity prevalence together with its devastating effects on health and associated comorbidities highlights the immediate need for pharmacological treatment, in addition to lifestyle changes and dietary reeducation [3-5]. In this context of pharmacological treatment, amphetamines were first synthesized in 1887 in German laboratories by chemical researcher Lazar Edeleanu. Over time, they began to be used for a variety of purposes due to their high potential for stimulating the central nervous system. The pharmaceutical industry has always known how to use this substance and transform it into various types of medications to treat various pathologies, such as fatigue, asthma, and nasal congestion [6].

During the Second World War, amphetamines were used to keep soldiers alert, thus distracting them from sleep and fatigue. Given the drug's great potential, illicit forms were created, such as methamphetamine (MDMA, ice, ecstasy), which was supposed to be administered to suppress appetite. Nowadays, amphetamine is a medicinal option for the controlled treatment of pathologies such as attention deficit hyperactivity disorder in children and narcolepsy, which is caused by a sleep disorder that causes excessive daytime sleepiness, cataplexy, and, in some situations, hallucinations [7,8].

It is known that the amount of anorectic drugs consumed increases when non-drug therapy, which includes physical exercise and dietary reeducation, does not achieve the desired effect for the patient. It is possible to observe that the use of anorectics in obese

people follows the trend of the obesity epidemic, given that women are the ones who consume the drugs the most. There are also studies indicating that amphetamine compounds are in fifth place among the most used drugs, both legally and illegally. However, obesity is not closely linked to amphetamine dependence, but to the greater incidence of vulnerability when the doses of the drug are higher for such patients. The recommended time for consumption to avoid risk is 8 to 12 weeks [8,9].

Furthermore, it is known that obesity treatment requires lifestyle changes and that drugs should be administered as a complementary alternative to treatment since they do not cure the disease, they only control it, given that significant and rapid weight loss occurs. Given the constant search for weight loss and standardized aesthetic purposes, a large part of the population resorts to treatment with anorectics, or as they are also known, appetite suppressants. Among them, the most sought-after are phentermine-topiramate, naltrexone-bupropion, lisdexamfetamine, methylphenidate, fenpropopex, sibutramine, mazindol, amfepramone, and lorcaserin, which, when used in different quantities and dosages, can suppress appetite [3,4]. In this sense, medications that cause weight loss by acting to inhibit appetite are called anorectics and are therefore called appetite suppressants/moderators or satiety agents. These drugs act by modulating catecholaminergic and/or serotonergic neurotransmissions [4,5].

Therefore, the present study carried out a systematic review to present the main scientific and clinical evidence of anti-obesity pharmacological treatments using anorectic drugs and their combinations.

METHODS

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: 04/11/2025. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: <https://amstar.ca/>. Accessed on: 04/11/2025.

Search Strategy and Search Sources

The literature search process was carried out from March to April 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo,

and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS/MeSH Terms) were used: "Anorectic drugs. Anti-obesity drugs. Obesity. Weight loss", and using the Boolean "and" between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

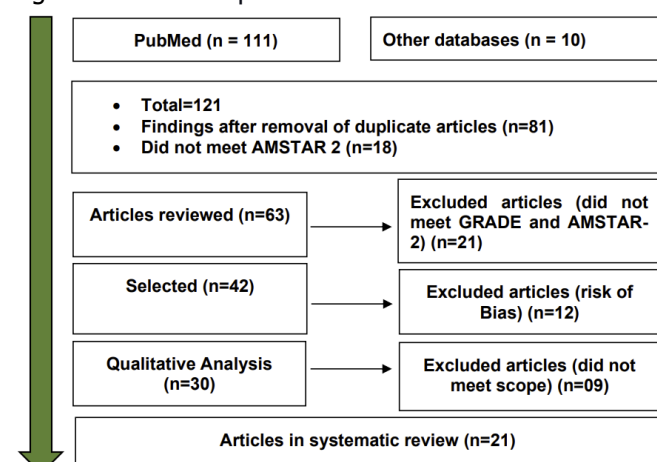
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials, prospective controlled studies, and retrospective observational studies. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

A total of 111 articles were found that were submitted to eligibility analysis, and 21 final studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2=78.7\% > 50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

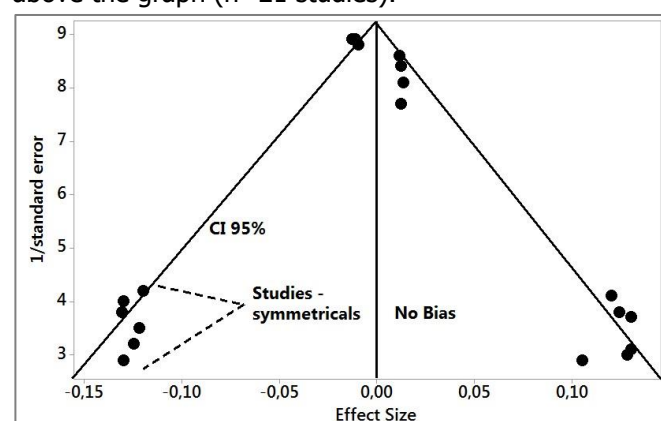
Figure 1. Selection process and inclusion of Articles.



Source: Own authorship.

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 Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among 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 shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=21 studies).



Source: Own authorship.

Key Clinical Findings – Obesity and Drugs

Pharmacotherapy offers an option for overweight and obese adults to reduce their body weight if lifestyle modifications fail. A systematic review and meta-analysis included randomized controlled trials of weight-loss medications in overweight and obese adults. A total of 14,605 citations were identified by the search, of which 132 eligible studies enrolled 48,209 participants. All medications reduced body weight compared with lifestyle modification alone; all subsequent figures refer to comparisons with lifestyle modification. High- to moderate-quality evidence established phentermine-topiramate as most effective for weight reduction (odds ratio [OR] for weight reduction $\geq 5\%$ 8.02, 95% CI 5.24 to 12.27; mean difference [MD] in percentage body weight change -7.98, 95% CI -9.27 to -6.69) followed by GLP-1 receptor agonists (OR 6.33, 95% CI 5.00 to 8.00; MD -5.79, 95% CI -6.34 to -5.25). Naltrexone-bupropion (OR 2.69, 95% CI 2.10 to 3.44), phenterminetopiramate (2.40, 1.68 to 3.44), GLP-1 receptor agonists (2.22, 1.74 to 2.84) and orlistat (1.71, 1.42 to 2.05) were associated with increased adverse events leading to drug discontinuation. In a post-hoc

analysis, semaglutide, a GLP-1 receptor agonist, showed substantially greater benefits than other drugs with a similar risk of adverse events as other drugs for likelihood of weight loss of 5% or more (OR 9.82, 95% CI 7.09 to 13.61) and percentage change in body weight (MD -11.40, 95% CI -12.51 to -10.29). In overweight and obese adults, phentermine-topiramate and GLP-1 receptor agonists are the best weight-loss medications; of the GLP-1 agonists, semaglutide may be the most effective [10].

A separate meta-analysis compared the benefits and harms of approved weight-control medications in overweight or obese adults. A total of 168 trials (97,938 patients) were included. No evidence approved weight-control medications had different associations with cardiovascular death (69 trials, 59,037 participants). The naltrexone/bupropion combination was associated with lower cardiovascular mortality than placebo (odds ratio [OR], 0.62 [95% CI: 0.39, 0.99]; low-quality evidence). All drugs were associated with greater weight loss at 12 months than placebo (33 trials, 37,616 participants), particularly semaglutide (mean difference [MD], -9.02 kg [95% CI: -10.42, -7.63]; moderate certainty) and phentermine/topiramate (MD, -8.10 kg [95% CI: -10.14, -6.05]; high certainty); and with a greater reduction in waist circumference at 12 months than placebo (24 trials, 35,733 participants), mainly semaglutide (MD, -7.84 cm [95% CI: -9.34, -6.34]; moderate certainty) and phentermine/topiramate (MD, -6.20 cm [95% CI: -7.46, -4.94]; moderate certainty). Semaglutide and phentermine/topiramate were associated with less or no difference in the odds of treatment discontinuation compared with all other drugs (87 trials, 70,860 participants) [11].

According to the findings, amfepramone and femproporex act by inhibiting appetite by increasing the activity of noradrenergic neurotransmission, by inhibiting the reuptake and/or increasing the release of noradrenaline. Mazindol acts by reducing food intake through noradrenergic and dopaminergic mechanisms. Sibutramine is in the second group, which promotes feelings of satiety and appetite inhibition due to the activation of serotonin and norepinephrine receptors [3-5,12].

Therefore, anorectic drugs have a mechanism of action similar to amphetamines, mainly associated with the stimulation that occurs in the central nervous system. The mechanism of action of anfepramone has a central action, which causes an increase in the production of norepinephrine and dopamine, stimulating the lateral hypothalamic nuclei and, therefore, inhibiting hunger. It is correct to state that anfepramone is the least harmful substance in cases of patients suffering from hypertension [13-16].

Femproporex is also a sympathomimetic central stimulant and reducer of the MAO enzyme. It acts directly on noradrenergic and dopaminergic neurotransmission and presynaptic vesicles, stimulating the release of neurotransmitters and inhibiting the release of dopamine reuptake in the feeding center, which is in the lateral hypothalamus. After administration, femproporex is biotransformed into amphetamine, to finally be eliminated [12].

Furthermore, mazindol is a drug that has origins in imidazoline (it does not have a phenethylamine group) and is similar to antidepressants, since it blocks the reuptake of norepinephrine and dopamine in nerve endings, modifying the peripheral energy mechanism and increasing glucose uptake by skeletal muscle. It cannot produce a feeling of euphoria; however, it has a low abuse potential when compared to other anorectics [5,12].

Sibutramine selectively reduces the reuptake of norepinephrine and serotonin. Its active metabolites block the serotonergic 5-HT₂, adrenergic (β), dopaminergic, and histamine (H₁) receptors, reducing their affinities. Unlike amphetamine, the metabolites released by sibutramine do not increase the release of neurotransmitters and do not reduce monoamine oxidase [4,14]. In this scenario, despite short-term weight loss with diet and exercise, weight regain remains a concern. Thus, these anti-obesity drugs may play a role in weight reduction. A meta-analysis of randomized clinical trials explored the efficacy and safety of anorectic drugs for weight reduction and subsequent treatment of obesity. It was observed that in the last five years of randomized studies, no significant overall complications were found, with only 5.7%. The mean overall weight loss was 6.18 (\pm 2.8) kg in the mean time of 12 months. The overall success rate among these drugs was 80.18%. The p-values showed no statistically significant difference, being $p < 0.05$ within each group of drugs analyzed, both for weight and success rates [17].

Obesity control guidelines strongly recommend lifestyle interventions along with medical treatment for overweight patients. Other recent meta-analyses of new anti-obesity drugs and their efficacy in weight loss have shown that overall placebo-subtracted weight reduction (%) for at least 12 months ranged from 2.9 to 6.8% for the following drugs: phentermine/topiramate (6.8%), liraglutide (5.4%), naltrexone/bupropion (4.0%), orlistat (2.9%), and lorcaserin (3.1%). However, in February 2020, the Food and Drug Administration (FDA) ordered the withdrawal of lorcaserin from the market, as a clinical trial to evaluate the drug's safety showed an increased risk of cancer [18].

Because successful long-term weight loss is difficult

to achieve and maintain in most patients with obesity through lifestyle modifications (e.g., diet, exercise, and behavioral therapy), pharmacologic approaches to obesity treatment should be considered as adjunctive therapy. Of note, four medications (orlistat, extended-release naltrexone/bupropion, controlled-release phentermine/topiramate, and liraglutide) can be used long-term (>12 weeks) to promote weight loss by suppressing appetite or decreasing fat absorption [19]. Furthermore, the American Gastroenterological Association guideline supports professionals in decisions about pharmacological interventions for overweight and obesity. Thus, a multidisciplinary panel of content experts and guideline methodologists used the Assessment, Development, and Evaluation of Recommendations Grading framework to prioritize clinical questions, identify patient-centered outcomes, and conduct an evidence synthesis for the following agents: semaglutide 2.4 mg, liraglutide 3.0 mg, extended-release phentermine-topiramate, naltrexone-bupropion, orlistat, phentermine, diethylpropion, and Gelesis100 oral superabsorbent hydrogel. The guideline panel made 9 recommendations. The panel strongly recommended the use of pharmacotherapy in addition to lifestyle interventions in adults with overweight and obese (body mass index ≥ 30 kg/m², or ≥ 27 kg/m² with weight-related complications) who have an inadequate response to lifestyle interventions. The panel suggested the use of semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate, and naltrexone-bupropion (based on moderate-quality evidence), and phentermine and diethylpropion (based on low-quality evidence), for long-term treatment of overweight and obesity. The guideline panel suggested against the use of orlistat. The panel identified the use of the oral superabsorbent hydrogel Gelesis100 as a knowledge gap [20].

A study evaluated the impact of the 2012 approval of phentermine/topiramate on subsequent topiramate use among patients with obesity. Enrollees were 18 to 65 years of age. Patients were required to have a diagnosis of obesity and no other condition that would justify topiramate use. Topiramate initiation rates were three times higher than phentermine/topiramate initiation rates during the post-approval period. The approval of phentermine/topiramate was associated with increased topiramate use among patients with obesity [21].

Phentermine/topiramate extended-release capsule (Qsymia®) is a fixed-dose combination of phentermine and topiramate that is being developed by VIVUS (a subsidiary of Icahn Enterprises) for the treatment of obesity, sleep apnea syndrome, type 2 diabetes mellitus, and nonalcoholic steatohepatitis (NASH). The once-daily formulation of phentermine (a sympathomimetic amine)

and topiramate was developed to combat obesity by decreasing appetite and increasing satiety. In July 2022, phentermine/topiramate received its first approval in the US as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in pediatric patients aged ≥ 12 years with an age- and gender-standardized BMI at or above the 95th percentile [22].

A study compared body weight reduction in kg (at 1 month) and development of tolerance (moT) at the first month of four interventions known to have low (placebo), intermediate (phentermine or mazindol monotherapy), and high (fixed-dose combination of 5 active ingredients) efficacy as predictors of their efficacy in reducing body weight at 6 months in percentage. In addition, a detailed analysis of 6- to 12-month follow-up of weight loss in individuals on orlistat or diet and exercise regimens was performed. The analysis included 662 adult individuals with obesity. The level of efficacy of the interventions in % body weight loss at 6 months was confirmed, although high overall variation was observed between individuals. Between 50 and 80% of participants who completed the 6- to 12-month follow-up maintained at least 5% % body weight loss [23].

Authors Grilo et al. (2024) [24] conducted a randomized, double-blind, placebo-controlled clinical trial on the efficacy of lisdexamfetamine (LDX) maintenance treatment as a maintenance treatment for responders to acute treatments with LDX alone or with cognitive behavioral therapy (CBT + LDX) for binge eating disorder (BED) in patients with obesity. A total of 61 (83.6% women, mean age 44.3, mean BMI 36.1 kg/m²) acute responders were randomized to LDX (N = 32) or placebo (N = 29) for 12 weeks; 95.1% completed post-treatment assessments. Relapse rates (to diagnostic-level binge-eating frequency) after maintenance treatments were 10.0% (N = 3/30) for LDX and 17.9% (N = 5/28) for placebo; intention-to-treat binge-eating remission rates were 59.4% (N = 19/32) and 65.5% (N = 19/29), respectively. Maintenance LDX and placebo did not differ significantly in binge eating but did differ in weight loss and eating disorder psychopathology. Maintenance LDX was associated with significant weight loss (-2.3%), while placebo had significant weight gain (+2.2%); LDX and placebo differed significantly in weight change during treatment and post-treatment. Eating disorder psychopathology remained unchanged with LDX but increased significantly with placebo.

Finally, LDX has shown significant scientific evidence for controlling binge eating and weight gain. However, only LDX is approved for the treatment of binge eating in some countries. Because obesity is a common consequence of binge eating disorder, medications that induce weight gain, such as the

atypical antipsychotics olanzapine or clozapine, the new antidepressant mirtazapine, and tricyclic antidepressants, and the mood stabilizer valproate, should be avoided whenever possible. In addition to LDX, tirzepatide, and retatrutide also stand out for the control of binge eating and its comorbidities [25].

Conclusion

It was concluded that the scientific findings of randomized clinical trials on the use of anorectic drugs for the treatment of obesity have shown safety and efficiency over the last five years, with reasonable weight loss and no significant complications. The combination of naltrexone-bupropion was significantly superior to placebo. Pharmacotherapy for obesity should be conducted according to an adequate assessment of clinical evidence and personalized for each patient, considering the characteristics of each medication and comorbidities associated with obesity. Adults with binge eating disorder and obesity who responded to acute treatment with lisdexamfetamine, regardless of whether they received additional cognitive-behavioral therapy, had good maintenance during the subsequent 12 weeks. Maintenance with lisdexamfetamine, compared to placebo, did not provide more benefits for binge eating but was associated with significantly better results for eating disorder psychopathology and greater weight loss.

CRedit

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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