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REVIEW ARTICLE

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Clinical outcome of off-label drugs for weight loss: a systematic review

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Abstract

Introduction: Obesity occurs when calorie intake and energy expenditure occur, causing serious comorbidities. According to the Ministry of Health, 52.5% of Brazilians are overweight. A variety of drug classes approved for other indications have been used off-label in attempts to promote weight loss. **Objective:** It was to carry out a systematic review to list the main drugs used off-label to treat obesity and its comorbidities, as well as present the results of clinical studies. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out 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 110 articles were found, and 29 articles were evaluated in full, and 18 were included and developed in the present systematic review study, out of a total of 20 (2 references are on the website and were not included) Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 21 studies with high risk of bias and 31 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=78.8%>50%. Off-label prescribing is very common among doctors who treat obesity. However, randomized controlled studies must be increasingly encouraged and increased to present scientific evidence and, thus, propose a scientific formalism for the safe and effective use of off-label anti-obesity drugs. Naltrexonebupropion was associated with significant improvements in binge eating disorder, with a consistent pattern of weight loss. In people without diabetes, tirzepatide resulted in substantial reductions in body weight (16.5% to 22.4%) over 72 weeks.

Keywords: Obesity. Off-label drugs. Diabetes mellitus. Weight loss.

Introduction

Obesity occurs when calorie intake and energy expenditure are at odds, causing serious comorbidities [1,2], and an estimated 2 billion people are overweight or obese worldwide [1]. Brazil ranks fifth in the world, with over 20 million obese people. According to the Ministry of Health, 52.5% of Brazilians are overweight [2].

In this context, after analyzing the Body Mass Index (BMI), the treatment of choice for excess weight (BMI>25 kg/m^2) and obesity (BMI>30 kg/m^2) should be physical activity, diet, and behavioral modifications. In cases of insignificant or unsatisfactory results, pharmacological treatment is justified [2]. The World Health Organization (WHO) recommends that the use of medications to combat obesity is indicated for patients with a body mass index (BMI) above 30 kg/m^2 or when the BMI is 25 kg/m2 associated with comorbidities [1]. In this scenario, a variety of drug classes approved for other indications have been used off-label in an attempt to promote weight loss [3].

ANVISA defines off-label use as "use in situations that deviate from the labeling of a drug registered with ANVISA. This may include differences in indication, age range/weight, dose, frequency, presentation, or route of administration" [2]. Notable among these drugs are anticonvulsants such as topiramate, drugs used to control diabetes, such as metformin, antidepressants such as fluoxetine and bupropion, naltrexone (for treating opioid dependence and alcoholism), tirzepatide, the hormone melatonin, etc. [3-5].

Prescribing medications for off-label use is not illegal; however, using a medication outside the recommended dosage range or duration of use can put patients' health at risk, as there is no scientific formality for this purpose [6]. Therefore, medications would be considered appropriate for off-label use based on their known clinical pharmacology and scientific evidence from clinical studies [4].

Therefore, the decision to use a medication off-label should be based on a careful assessment of the patient's treatment history and the potential risks and benefits of the medication. Patients should receive appropriate informed consent regarding how the medication is being used off-label and why, along with proper information about known risks and side effects [6]. Over the past 20 years, the U.S. Food and Drug Administration (FDA) has approved nine medications for the treatment of obesity. Phentermine is approved by the FDA only for short-term use and is used off-label for long-term use [7].

Therefore, this study conducted a systematic review to present the main drugs used off-label for the treatment of obesity and its comorbidities, as well as the outcomes of clinical studies.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: April 14, 2025. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: April 14, 2025.

Data Sources and Search Strategy

The literature search process was conducted 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 descriptors (DeCS / MeSH Terms) were used: *"Obesity. Off-label drugs. Diabetes mellitus. Weight loss"*, and using the Boolean "and" between the MeSH terms and "or" between the historical discoveries.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding risk of bias, clarity of comparisons, precision, and consistency of analyses. The most prominent findings were systematic reviews or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size) using Cohen's d test.

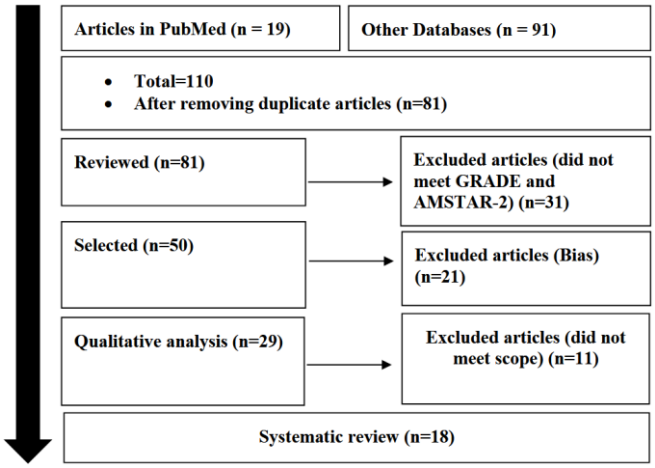
Results and Discussion

Summary of Findings

A total of 110 articles were found and submitted for eligibility analysis, with 18 final studies selected to comprise the results of this systematic review, out of a total of 20 (two references are websites that were not included in the risk of bias analysis). The selected studies were of medium to high quality (Figure 1), considering the level of scientific evidence from studies such as meta-analysis, consensus, randomized clinical trials, prospective, and observational studies. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies

presented homogeneous results, with X^2=78.8%>50%. Using the Cochrane risk of bias tool, the overall assessment resulted in 21 studies with a high risk of bias and 31 studies that did not meet the GRADE and AMSTAR-2 criteria.

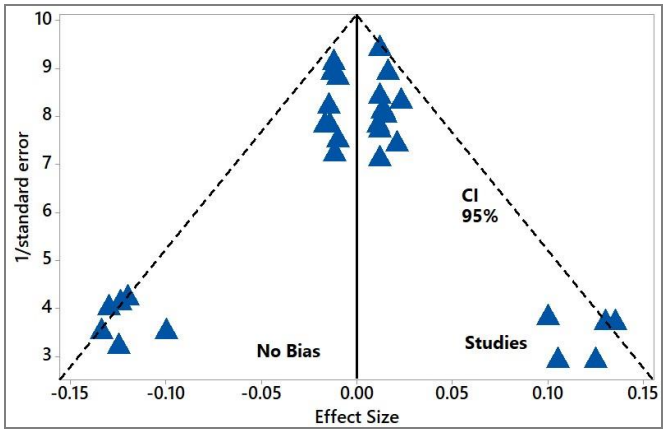
Figure 1. Selection of articles by exclusion based on GRADE and AMSTAR-2.



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 d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph exhibited symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), shown at the bottom of the graph, or among studies with large sample sizes, shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes, shown at the bottom of the graph. High-confidence and high-recommendation studies are shown above the graph (n=18 studies).



Source: Own authorship.

Main Clinical Outcomes

Off-Label Drugs for the Treatment of Obesity

It is important to emphasize that the longer a drug is in use, the greater the likelihood that its safety and efficacy will become known, even if not previously considered during the approval process. Long-term use may demonstrate that initial safety warnings in the labeling are unfounded. Therefore, the information contained in the labeling of older drugs may be outdated due to the unavailability of more recent clinical research and proven scientific evidence **[5,8-18]**. Table 1 below presents the main anti-obesity drugs used off-label. The following section presents the main clinical studies regarding the safety and efficacy of some of the off-label anti-obesity drugs.

Table 1. Main off-label drugs in anti-obesity.

Off-Label Drugs	Prescription	Dose Anti-obesity	Bias
Fluoxetine [8]	- Serotonergic agent; - Antidepressant;	60 mg	Dose-related effect on weight loss. Help with short-term weight loss;
Duloxetine [8]	- Treatments for major depressive disorders, painful diabetic neuropathy, and urinary incontinence		Although it significantly reduces food intake, there is still a lack of scientific evidence from randomized studies.
Topiramate [16]	- Epilepsy; - Lennox-Gastaut syndrome; - Migraine	64 mg to 384 mg	Although the exact mechanism of its action in managing weight loss is not known, Topiramate has been tested as an adjunct to treat obesity and appears to be reasonably well tolerated.
Bupropione and Naltrexone [5,14]	This combination is approved for use in the US, but here we can use it by prescribing the medications separately. Bupropion acts on adrenergic and dopaminergic receptors in the hypothalamus, and naltrexone is an opioid receptor antagonist. Bupropion is indicated on the label for the treatment of smoking, depression, and anxiety. Naltrexone, on the other hand, is originally used to treat alcoholism and counteract the effects of some medications. Alone, they have little effect on weight loss, but their combined action leads to synergistic action on POMC neurons (an important hypothalamic anorexigenic center) with good results, with up to 5% greater weight loss than in the placebo group. The most common adverse reactions are nausea, constipation, headache, vomiting, and dizziness.	Bupropione: 300 mg/day a 600 mg/day; Naltrexone: 50 mg/day.	Clinical studies show that bupropion can cause both weight loss and weight gain, although with different incidences.
Lisdexamfetamine [9]	-Dextroamphetamine prodrug, -Promotes the release of monoamine neurotransmitters.	50 mg or 70 mg diaries	Safety and efficacy have not been established for the treatment of obesity.
Phentermine [9] (long term)	*- Long-term off-label. It is an amphetamine derivative, used primarily as an appetite suppressant.*		Its potential long-term adverse effects have not been proven.
Metformin [4]	Type 2 diabetes treatment.	850 mg three times daily (2,550 mg/day)	Although it is not an approved indication, evidence suggests its effectiveness. Studies have also been conducted with metformin to treat weight gain induced by antipsychotic treatment.
Semaglutide [8]	It is used, in conjunction with diet and exercise, to treat adult patients with poorly controlled type 2 diabetes.	4 mg in 3 mL.	Although it has demonstrated a weight loss effect, clinical studies were only carried out with diabetic patients.
Exenatide [7]	-Diabetes treatment	5 to 10 mcg, 2 times a day	Safety and efficacy have not been established for the treatment of obesity.
Zonisamide [17]	- Approved for epilepsy, this medication induces weight loss and has been used off-label or in combination with bupropion or phentermine.	400 mg	Safety and efficacy have not been established for the treatment of obesity.
Pramlinitide [15]	-Diabetes treatment.	120 mcg	Although it can promote weight loss in non-diabetic patients, there is still no scientific evidence of its effectiveness.
Metreleptin [7]	- Approved for congenital or acquired generalized lipodystrophy. -Metreleptin is a synthetic analogue of leptin.	10 mg (2 mL)	Leptin administration after weight loss in obese patients may reverse some of the neuroendocrine adaptations involved in weight regain. However, studies are scarce.
Melatonin [18]	- Sleep disorders.	1 to 10 mg	Few clinical studies.

Tirzepatide [5]	It is intended as an adjunctive treatment to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Tirzepatide is the first dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist.	Starting dose: 2.5 mg once weekly. After 4 weeks, the dose should be increased to 15 mg/week.	It can lead to nausea, vomiting, gastrointestinal changes, even constipation, diarrhea, depending on the person, and very rarely even hypoglycemia.

Source: Own authorship.

Binge eating disorder, the most prevalent eating disorder, is a serious public health problem associated with obesity. Grilo et al. (2022) **[19]** conducted a randomized, doubleblind, placebo-controlled study to analyze the efficacy of naltrexone-bupropion and behavioral therapy for weight loss (BWT), alone and in combination, for BWD comorbid with obesity. A total of 136 patients with BWD (81.6% women; mean age, 46.5 years; mean BMI, 37.1) were randomized to one of four 16-week treatments: placebo (N=34), naltrexone-bupropion (N=32), BWT+placebo (N=35), or BWT+naltrexone-bupropion (N=35). Overall, 81.7% of participants completed independent post-treatment assessments. Intention-to-treat binge eating remission rates were 17.7% in the placebo group, 31.3% in the naltrexone-bupropion group, 37.1% in the PP+placebo group, and 57.1% in the PP+naltrexone-bupropion group. Logistic regression of binge eating remission revealed that naltrexone-bupropion was significantly superior to placebo. Rates of participants achieving 5% weight loss were 11.8% in the placebo group, 18.8% in the naltrexone-bupropion group, 31.4% in the PP+placebo group, and 38.2% in the PP+naltrexone-bupropion group. Mixed models revealed significantly greater improvements for weight loss on secondary measures (eating disorder psychopathology, depression, eating behaviors, and cholesterol and HbA1c levels).

Furthermore, tirzepatide is the first dual GLP-1/GIP receptor co-agonist approved for the treatment of type 2 diabetes mellitus (T2DM) based on results from the SURPASS program. The SURPASS trials evaluated the safety and efficacy of tirzepatide in people with T2DM, from monotherapy to the addition of insulin in global populations, with two other trials dedicated to the Japanese population. Over treatment periods of up to 104 weeks, tirzepatide 5 to 15 mg once weekly reduced glycosylated hemoglobin (1.87% to 3.02%), body weight (5.4 to 12.9 kg), and improved multiple cardiometabolic risk factors (including reductions in liver fat, new-onset macroalbuminuria, blood pressure, and lipids) across the T2DM spectrum. Tirzepatide provided better efficacy than placebo and other commonly used glucose-lowering medications, such as semaglutide 1 mg, dulaglutide, insulin degludec, and glargine. All doses of tirzepatide were well tolerated, with a side effect profile similar to that of GLP-1 receptor analogs **[20]**.

The first clinical trial on the effect of metformin was conducted in the US in 2005 in 10 non-insulin-dependent diabetic patients. The results of this study explained the primary metabolic effect of metformin on the liver through inhibition of gluconeogenesis, along with a weight-loss effect involving adipose tissue **[10]**. Subsequently, another randomized clinical trial in 27 centers in 2002 showed that metformin significantly reduced weight in non-diabetic patients. In 2005, the first experimental study deduced that metformin clearly improved insulin resistance resulting from high-fat intake through the activation of AMP-activated protein kinase subunit 2 (AMPK2) in rat skeletal muscle. Importantly, a study conducted from 2009 to 2013 to evaluate metformin prescription patterns in adolescents in the United States showed its off-label use in approximately 6.5% of those diagnosed with obesity. In 2013, the first published study demonstrated that metformin up to a dose of 2500 mg per day is an effective medication for weight reduction in 154 non-diabetic outpatients with a body mass index greater than 27 kg/m2 **[10]**.

Subsequently, a six-month randomized clinical trial concluded that metformin 1000mg twice daily is useful in the treatment of obesity. Several studies have also illustrated the mechanism of metformin's action in obesity. However, the main pathway metformin uses to induce weight loss is through adipose tissue loss, coupled with the regulation of energy expenditure through exercise. In this context, cyclin-dependent kinase 4 (CDK4), a protein involved in cell division, regulates cellular energy balance by directly controlling AMPK2 activity. Furthermore, CDK4 suppresses fatty acid oxidation through direct phosphorylation and inhibition of AMPK2. Furthermore, CDK4 is an important participant in insulin signaling in white adipose tissue, contributing to the development of obesity related to insulin resistance through elevated fatty acid levels. Clinically, AMPK2 is a critical regulator of cellular consumption processes, triggering catabolic pathways for ATP output. Therefore, it appears that AMPK2 is one of the possible targets of metformin for the treatment of obesity. However, an unanswered question remains regarding the possibility of metformin targeting CDK4 in normal obese patients to produce its major pathway through adipose tissue **[10]**.

Also, fluoxetine is a serotonin reuptake inhibitor indicated for major depression. It is also believed to affect weight control through changes in appetite, resulting in reduced food intake and normalization of unusual eating behaviors. However, the riskbenefit ratio of this off-label medication is unclear. Therefore, a study evaluated the effects of fluoxetine in

overweight or obese adults. Randomized controlled trials comparing fluoxetine versus placebo, other anti-obesity agents, non-pharmacological therapy, or no treatment in overweight or obese adults without depression, mental illness, or abnormal eating patterns were included. The trials were assessed for overall certainty of evidence using the GRADE instrument. Random-effects meta-analyses were performed, and risk ratios (RR) with 95% confidence intervals (95% CI) were calculated for dichotomous outcomes and mean differences (MD) with 95% CI for continuous outcomes. We identified 1036 records, reviewed 52 full-text articles, and included 19 completed randomized trials. A total of 2216 participants entered the trials; 1280 participants were randomly assigned to fluoxetine (60 mg/day, 40 mg/day, 20 mg/day, and 10 mg/day), and 936 participants were randomly assigned to various comparison groups (placebo; the anti-obesity agents diethylpropion, fenproporex, mazindol, sibutramine, metformin, fenfluramine, dexfenfluramine, fluvoxamine, 5hydroxytryptophan; no treatment; and omega-3 gel). Within the 19 randomized studies, there were 56 trial arms. Fifteen trials were conducted in parallel randomized clinical trials, and four in crossover randomized clinical trials. Participants in the included studies were followed for periods ranging from three weeks to one year. The certainty of the evidence was low or very low. Most studies had a high risk of bias in one or more domains **[12]**.

Additionally, patients with type 1 diabetes often have suboptimal glycemic control. The gold standard of treatment is basal-bolus insulin or subcutaneous insulin infusion via an insulin pump. Although insulin therapy improves glycemic control, weight gain and hypoglycemia often limit the achievement of hemoglobin A1C goals. The number of people with type 1 diabetes who are overweight or obese is increasing, and there are many similarities between what was historically called type 1 and type 2 diabetes. Thus, one study examined the use of antihyperglycemic agents that target other pathophysiological abnormalities to facilitate weight loss and improve glycemic control. A MEDLINE search from 1975 to October 2018 was conducted to identify articles that studied non-insulin agents in adults with type 1 diabetes and a body mass index (BMI) ≥25 kg/m2. Identified articles were included if the study duration was ≥4 weeks, included ≥20 patients, and established a mean baseline BMI ⩾of 25 kg/m2. This review analyzed 32 clinical trials. Amylin mimetics, glucose-sodium transporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists demonstrate the greatest improvements in body weight and hemoglobin A1C. Therefore, the addition of non-insulin antihyperglycemic agents may benefit the selection of overweight or obese adults with type 1 diabetes. These agents are off-label, and if used, close monitoring is essential **[13]**.

Bupropion is an atypical antidepressant that unduly causes weight loss. Although the average weight loss observed with bupropion is small, as an antidepressant, it is preferable to many medications that can induce weight gain. Anderson et al. **[14]** conducted a 48-week, randomized, placebo-controlled study investigating the efficacy of bupropion in promoting weight loss. There were three study arms: placebo, 300 mg, and 400 mg of sustained-release bupropion. The percentage losses from baseline body weight for individuals completing 24 weeks were 5.0%, 7.2%, and 10.1% for placebo, 300 mg, and 400 mg sustained-release bupropion, respectively. In obese individuals with depressive symptoms, sustained-release bupropion was more effective than placebo in weight loss when combined with a 500-kcal deficit diet (4.6% vs. 1.8% loss of baseline body weight, $p < 0.001$). Bupropion is contraindicated in patients with seizures.

Pramlintide acetate is an injectable agent approved by the FDA for the treatment of type 1 and type 2 diabetes. Pramlinitide mimics the action of the pancreatic hormone amylin, which, along with insulin, regulates postprandial glucose control. Its effect on weight loss is thought to be mediated by central (brain) receptors that improve appetite control. In a pooled post-hoc analysis of overweight and obese insulin-treated patients with type 2 diabetes, pramlinitide-treated patients (receiving 120 mg twice daily) had a reduction in body weight of -1.8 kg ($p<0.0001$) compared with placebo-treated patients. In this study, pramlinitide-treated patients showed a 3-fold increase in successfully achieving a total body weight loss of>5% when compared with those receiving a placebo. Subsequently, randomized trials combining pramlinitide or placebo with a lifestyle intervention were conducted in obese participants without diabetes. Treatment with pramlinitide (up to 240 mg three times daily) for 16 weeks resulted in a placebo-corrected reduction in body weight of 3.7% ($p<0.001$), and 31% of pramlinitide-treated individuals achieved ≥5% weight loss vs. 2% with placebo ($p<0.001$). In another study with one year of follow-up, placebo-corrected weight loss in those taking 120 mg three times daily and 360 mg twice daily averaged 5.6% and 6.8% (both $p<0.01$). Nausea was the most common adverse event with pramlinitide treatment in these studies **[15]**.

Furthermore, topiramate is an antiepileptic agent that reduces body weight in patients with a variety of

disorders, including epilepsy, bipolar disorder, and binge-eating disorder. Randomized controlled trials have demonstrated that topiramate has been reported to be tolerable and effective in promoting weight loss. In addition to its use for epilepsy, topiramate has received FDA approval for the prevention of migraines. Topiramate has also been used off-label for the treatment of neuropathic pain, as it causes weight loss rather than the weight gain typically seen with other antiepileptic agents. Topiramate can cause paresthesia, cognitive side effects, as well as kidney stones and, rarely, acute angle-closure glaucoma **[16]**.

Zonisamide is another antiepileptic medication that also reduces body weight in patients. Randomized controlled trials, both short-term (16 weeks) and longer-term (one year), in obese patients have shown that 400 mg of zonisamide daily is effective in promoting modest weight loss (~5 kg placebo-subtracted weight). The most commonly reported side effects compared to placebo were gastrointestinal (nausea/vomiting), nervous system (headaches), and cognitive (anxiety, impaired memory, language problems). Zonisamide should not be administered to patients hypersensitive to sulfonamides **[17]**.

Finally, melatonin is a hormone produced primarily by the pineal gland, but also in the gastrointestinal tract, retina, lacrimal glands, skin, erythrocytes, platelets, lymphocytes, and bone marrow mononuclear cells, derived from the noradrenergic stimulation of tryptophan and serotonin by α1 and β1 adrenergic receptors in postsynaptic pinealocytes. A study of brown adipose tissue in patients with melatonin deficiency (radiotherapy or surgical removal of the pineal gland) before and after daily melatonin replacement (3 mg) for 3 months. In this case, there was an increase in brown adipose tissue volume and activity measured by positron emission tomography. Improvements in blood levels of total cholesterol and triglycerides were also observed. It was concluded that oral melatonin replacement increases brown adipose tissue volume and activity, as well as promoting improvements in the lipid profile in individuals with melatonin deficiency **[18]**.

Conclusion

It was concluded that off-label prescribing is very common among physicians treating obesity. However, randomized controlled trials should be increasingly encouraged and expanded to clearly present the scientific evidence and, thus, provide a scientific framework for the safe and effective use of off-label anti-obesity drugs. Naltrexone-bupropion was associated with significant improvements in binge-eating disorder, with a consistent pattern of weight loss. In individuals without diabetes, tirzepatide resulted in substantial reductions in body weight (16.5% to 22.4%) over 72 weeks.

CRediT

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Application of Artificial Intelligence (AI)

Not applicable.

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It was performed.

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