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REVIEW ARTICLE

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Off-label pharmacotherapy of obesity: a systematic review

Roger Rafael Porto Rocha[1,2*], Tamara Caetano[3,4]

[1] RR Nucleus. Aurelio José Marques Street, 77, Downtown – Irece, Bahia, Brazil.
[2] Hospital for ICU Operations. Aurelio José Marques Street, 77, Downtown – Jequié, Bahia, Brazil.
[3] São José Municipal Hospital. Anita Gabribaldi Avenue, 238, Joinville, Santa Catarina, Brazil.
[4] Dona Helena Hospital. Blumenau Street, 123, Downtown, Joinville Santa Catarina, Brazil.

*Corresponding author: Roger Rafael Porto Rocha. RR Nucleus. Aurelio José Marques Street, 77, Downtown, Irece, Bahia, Brazil, and Hospital for ICU Operations. Aurelio José Marques Street, 77, Downtown, Jequié, Bahia, Brazil.
E-mail: rogerrafael_@hotmail.com

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Abstract

Introduction: In the context of obesity pharmacotherapy, some anti-obesity medications (monoamine oxidase inhibitors - MAOIs) have been approved by the Federal Drug Administration (FDA). MAOIs is indicated in combination with lifestyle changes to control overweight and obesity. Some drugs used off-label are accumulating evidence for weight management. **Objective:** It was to carry out a systematic review to present the off-label pharmacotherapy of obesity through the outcomes of clinical studies. **Methods:** The present study followed a concise systematic review model (PRISMA). The literary search process was carried out from May to July 2023 and developed based on Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2023. The 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 using the Funnel Plot chart. **Results and Conclusion:** It was found 132 studies that were submitted to the eligibility analysis and, then, 16 of the 48 total studies were selected. Most studies showed homogeneity in their results, with X^2 =95.1% >50%. The Funnel Plot graph showed a symmetrical behavior, not suggesting a significant risk of bias in the studies. Some drugs used off-label are accumulating evidence for weight management. As an example, tirzepatide is a new drug approved by the FDA in May 2022 for the treatment of type 2 diabetes mellitus and can be used off-label for the treatment of obesity. In 2013, the first published study showed that metformin up to a dose of 2500 mg per day is an effective medication to reduce weight. AMPK2 is one of the possible targets of metformin for the treatment of obesity. Although metformin treatment in participants receiving a placebo appears to result in an initial decrease in BMI and HOMA-IR, there is no evidence of a sustained effect after prolonged use in adolescents. Low-certainty evidence suggests that off-label fluoxetine may decrease weight compared with placebo. Sustained-release bupropion was more effective than placebo in weight loss when combined with a 500 kcal deficit diet. 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%, and 31% of subjects treated with pramlinitide achieved ≥5% weight loss vs. 2% with placebo. Oral melatonin replacement increases the volume and activity of brown adipose tissue, promoting thermogenesis and adipose tissue metabolism with consequent weight loss.

Keywords: Obesity. Pharmacotherapy. Off-label pharmacotherapy. Clinical studies.

Introduction

In the context of obesity pharmacotherapy, some anti-obesity drugs (monoamine oxidase inhibitors - MAOIs) have been approved by the Federal Drug Administration (FDA) for the long-term treatment of obesity. MAOIs are indicated in combination with lifestyle changes to control overweight and obesity. Current

guidelines recommend that individuals who have attempted lifestyle changes and continue to have a body mass index (BMI) of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with obesity-related comorbidity be eligible for medication treatment for weight loss. Some medications used off-label are accumulating evidence for weight control **[1]**. The World Health Organization (WHO) recommends that the use of drugs to combat obesity is indicated for patients who have a body mass index (BMI) above 30 kg/m^2 or when the BMI is 25 kg/m^2 associated with comorbidities that permeate overweight **[2]**.

In this sense, the debate about the options for pharmacological treatment of obesity continues. A variety of classes of drugs approved for other indications have been used off-label in an attempt to promote weight loss **[3-9]**. In this regard, off-label use is defined by ANVISA as "the use in situations that differ from the package insert of a drug registered with ANVISA. It may include differences in indication, age range/weight, dose, frequency, presentation or route of administration" **[3]**. Among these drugs, the most notable are anticonvulsants, such as topiramate, drugs used to control diabetes, such as metformin and tirzepatide as a new drug approved by the FDA **[10]**, antidepressants, such as fluoxetine and bupropion, and the hormone melatonin **[11]**. Thus, prescribing medications for off-label use is not illegal; however, using a medication outside the recommended dosage range or duration of use may put patients' health at risk, given that there is no scientific formalism for this **[4,11-14]**.

Medications would be considered appropriate for off-label use, based on their known clinical pharmacology and scientific evidence from clinical studies **[15-17]**. The decision to use an off-label medication should be based on a careful assessment of the patient's treatment history and the potential risks and benefits of the medication.

In this sense, patients should receive adequate informed consent about how the medication is being used off-label and why, along with appropriate information about known risks and side effects **[4]**. In the last 20 years, the US FDA has approved 9 medications to treat obesity. Phentermine is approved by the FDA only for short-term use and is used off-label for long-term use **[5]**.

Therefore, the present study aimed to carry out a systematic review to present off-label pharmacotherapy for obesity through the outcomes of clinical studies.

Methods

Study Design

The systematic review rules of the PRISMA Platform were followed. Available at: www.prisma-statement.org/. Accessed on: 06/15/2023.

Data Sources and Search Strategy

The search strategies for this systematic review were based on the health science descriptors (DeCS/MeSH Terms): "Obesity. Pharmacotherapy. Off-label pharmacotherapy. Clinical studies". The search was conducted from May to July 2023 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of the keywords with the Boolean operators "OR", "AND" and the "NOT" operator was used to target the scientific articles of interest.

Study Quality and Risk of Bias

The quality of the studies was based on the GRADE instrument, prioritizing studies with scientifically rigorous methodology, randomized clinical studies, and clinical and/or preclinical studies with a significant sample size. The risk of bias was analyzed according to the Cochrane instrument.

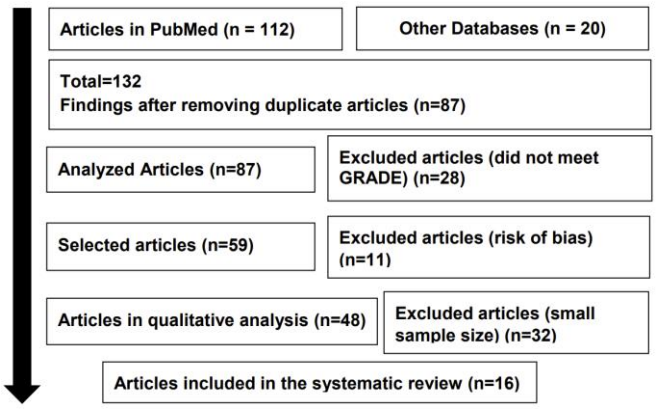
Results and Discussion

Summary of Findings

A total of 132 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the topic of this article, resulting in 87 articles. A total of 48 articles were evaluated in full and 16 were included and developed in the present systematic review study

(Figure 1), except for 2 references that are websites of Government Institutions (WHO and ABESO). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 11 studies with a high risk of bias and 28 studies that did not meet GRADE. Most studies presented homogeneity in their results, with X^2 =95.1% >50%.

Figure 1. Flowchart showing the article selection process.

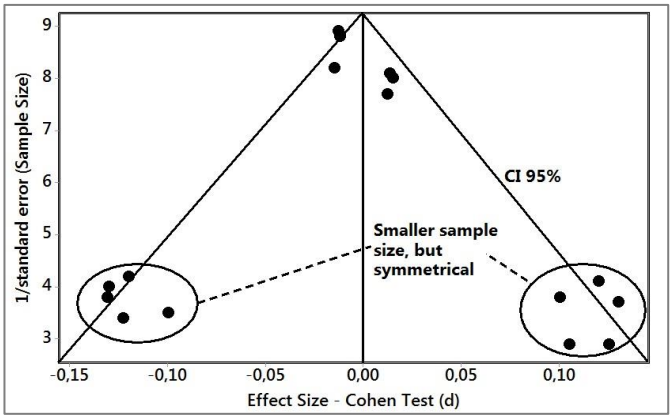


Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Magnitude of the difference (Effect

size) using Cohen's Test (d). The sample size was determined indirectly by the inverse of the standard error. This graph showed symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are shown in the upper region.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (NTotal = 16 studies evaluated in full in the systematic review).

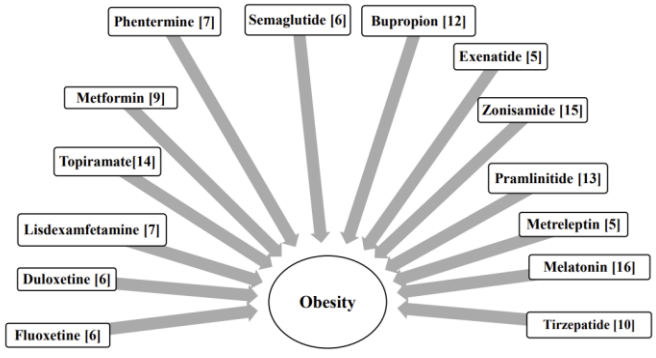


Source: Own Authorship.

Off-Label Pharmacological Treatment of Obesity

It is known that the longer a drug is in use, the greater the likelihood of discovering its safety and efficacy that was not previously considered or even during the approval process. Long-term use may demonstrate that the initial safety warnings in the package insert are unfounded. Therefore, the information contained in the package inserts of older drugs may be outdated due to the unavailability of more recent clinical research and proven scientific evidence. Figure 3 shows the main anti-obesity drugs used off-label.

Figure 3. Off-label drugs for the treatment of obesity.



Source: Own Authorship.

Key Clinical Outcomes

In the setting of pharmacological treatment of obesity, tirzepatide is a new drug approved by the FDA in May 2022 for the treatment of type 2 diabetes mellitus and can be used off-label for the treatment of obesity. It functions as a GLP-1 and GIP agonist to maximize benefits similar to those seen with GLP-1 drugs such as semaglutide. Tirzepatide is administered as a subcutaneous injection once a week. The most commonly reported adverse effects are gastrointestinal, such as nausea or diarrhea **[10]**.

In addition, bupropion has been approved by the FDA since 1985 for the treatment of depression in adults, seasonal affective disorder, and smoking cessation. Off-label and non-FDA-approved uses include antidepressant-induced sexual dysfunction, attention-deficit/hyperactivity disorder (ADHD), depression associated with bipolar disorder, and obesity. In the pediatric population, bupropion is used off-label for ADHD **[18]**.

The first clinical trial on the effect of metformin was conducted in the USA in 2005 in 10 non-insulin-dependent diabetic patients. The result of this study explained the primary metabolic effect of metformin on the liver by inhibition of gluconeogenesis alongside a weight loss effect involving adipose tissue. Then, 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 improved insulin resistance resulting from high fat intake through activation of AMP-activated protein kinase subunit 2 (AMPK2) in rat skeletal muscle. It is important to note that 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 reducing weight in 154 non-diabetic outpatients with a body mass index greater than 27 kg/m^2 **[8]**.

Subsequently, a six-month randomized clinical trial concluded that metformin 1000 mg twice daily is useful in the treatment of obesity. Also, several studies have illustrated the mechanism of action of metformin in obesity **[7]**. However, the major pathway of metformin that induces weight reduction is through the loss of adipose tissue alongside the regulation of energy expenditure with exercise. In this context, cyclin-dependent kinase 4 (CDK4), a protein that participates in cell division, organizes the balance of cellular energy through direct control of AMPK2 activity. In addition, 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 that contributes to the development of obesity-related to insulin resistance through the elevation of fatty acids. Clinically, AMPK2 is the critical regulator of cellular consumption operations, triggering the catabolic pathways of ATP output. Therefore, it seems that AMPK2 is one of the possible targets of metformin for the treatment of obesity. However, a question remains unanswered related to the possibility of metformin targeting CDK4 in normal obese patients to produce its major pathway via adipose tissue **[8]**.

Furthermore, metformin is widely used in the treatment of obesity. However, studies on long-term metformin treatment in obese patients are scarce. Therefore, an 18-month open-label extension study was conducted after an 18-month randomized placebo-controlled trial (RCT) on the efficacy, safety, and tolerability of metformin in adolescents with obesity and insulin resistance. After completion of the RCT, metformin was offered to all participants with a body mass index standard deviation (BMI-sds) score >2.3 and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) ≥3.4. Endpoints were changes in BMI and HOMA-IR. Overall, 31/42 participants completed the extension study (74% girls, mean age 14.8 (11.6 - 17.9), BMI 31.2 (22.3 - 45.1), HOMA-IR 3.4 (0.2 - 8.8). At baseline, 22/42 (52.4%) participants were eligible for metformin, of whom 13 (59.0%) agreed to treatment. In participants continuing metformin, an increase in BMI (+2.2) and HOMA-IR (+13.7) was observed. In participants receiving a placebo, BMI stabilized after an initial decrease (+0.5). For HOMA-IR, a decrease (-1.1) was observed. Although metformin treatment in participants receiving a placebo appears to result in an initial decrease in BMI and HOMA-IR, there is no evidence of a sustained effect after long-term use in adolescents. Limited adherence and/or insufficient dosage may explain the differences in long-term effects between adolescents and adults **[9]**.

Also, fluoxetine is a serotonin reuptake inhibitor indicated for major depression. It is also thought to affect weight control through changes in appetite, resulting in reduced food intake and normalization of unusual eating behaviors. However, the risk-benefit ratio of this off-label medication is unclear. Thus, one study evaluated the effects of fluoxetine in overweight or obese adults. Randomized controlled trials comparing fluoxetine versus placebo, other antiobesity agents, nonpharmacological therapy, or no treatment in overweight or obese adults without depression, mental illness, or abnormal eating patterns were included. 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. It was 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 agent's diethylpropion, fenproporex, mazindol, sibutramine, metformin, fenfluramine, dexfenfluramine, fluvoxamine, 5-hydroxytryptophan; no treatment; and ômega-3 gel). Within the 19 randomized trials, 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 of the domains **[11]**.

Thus, in this study comparing fluoxetine versus placebo, across all dosages and durations of fluoxetine treatment, the MD was -2.7 kg (95% CI -4 to -1.4; $p < 0.001$; 10 trials, 956 participants; low-certainty evidence). The 95% prediction interval ranged from -7.1 kg to 1.7 kg. The MD in reducing body mass index (BMI) across all dosages of fluoxetine compared with placebo was -1.1 kg/m² (95% CI -3.7 to 1.4; 3 trials, 97 participants; very low-certainty evidence). Only nine placebo-controlled trials reported adverse events. A total of 399 of 627 participants (63.6%) receiving fluoxetine compared with 352 of 626 participants (56.2%) receiving placebo experienced an adverse event. Random-effects meta-analysis showed an increased risk of at least one adverse event of any type in the fluoxetine groups compared with placebo (RR 1.18, 95% CI 0.99 to 1.42; p=0.07; 9 studies, 1253 participants; low-certainty evidence). The 95% prediction interval ranged from 0.74 to 1.88 **[11]**.

Also in this study, after treatment with fluoxetine, the adverse events of dizziness, somnolence, fatigue, insomnia, and nausea were observed approximately twice as often as with placebo. A total of 15 of 197 participants (7.6%) receiving fluoxetine compared with 12 of 196 participants (6.1%) receiving placebo experienced depression. The RR across all doses of fluoxetine compared with placebo was 1.20 (95% CI 0.57 to 2.52; p=0.62; 3 trials, 393 participants; very low-certainty evidence). All-cause mortality, health-related quality of life, and socioeconomic outcomes were not reported. Comparisons of fluoxetine with other antiobesity agents (3 trials, 234 participants), omega-3

gel (1 trial, 48 participants), and no treatment (1 trial, 60 participants) showed inconclusive results (very low-certainty evidence). Therefore, low-certainty evidence suggests that off-label fluoxetine may decrease weight compared with placebo. However, low-certainty evidence suggests an increased risk of dizziness, somnolence, fatigue, insomnia, and nausea after fluoxetine treatment **[11]**.

Patients with type 1 diabetes often have suboptimal glycemic control. The gold standard of care 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 pathophysiologic abnormalities to facilitate weight loss and improve glycemic control. A MEDLINE search from 1975 through October 2018 was performed to identify articles that studied noninsulin agents in adults with type 1 diabetes and a body mass index (BMI) ≥25 kg/m^2. Identified articles were included if the study duration was ≥4 weeks, included ≥20 patients, and established a mean baseline BMI ⩾of 25 kg/m^2. This review analyzed 32 clinical trials. Amylin mimetics, sodium-glucose 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 **[12]**.

Moreover, bupropion is an atypical antidepressant that unduly induces weight loss. Although the mean weight loss observed with bupropion is small, as an antidepressant it is preferable to many medications that can induce weight gain. Anderson et al.**[13]** 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 sustained-release bupropion. The percentage losses from baseline body weight for subjects completing 24 weeks were 5.0%, 7.2%, and 10.1% for placebo, 300 mg, and 400 mg sustained-release bupropion, respectively. In obese subjects with depressive symptoms, sustained-release bupropion was more effective than placebo for 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.

Additionally, pramlinitide acetate is an FDA-approved injectable agent for the treatment of type 1 and type 2 diabetes. Pramlintide mimics the action of the pancreatic hormone amylin, which, together 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 post-hoc pooled analysis of overweight and obese insulin-treated patients with type 2 diabetes, patients treated with pramlintide (receiving 120 mg twice daily) had a -1.8 kg (p<0.0001) reduction in body weight compared with placebo-treated patients. In this study, patients treated with pramlinitide had a 3-fold increase in successfully achieving >5% total body weight loss compared with those receiving placebo. Subsequent randomized trials combining pramlintide or placebo with a lifestyle intervention have been conducted in obese participants without diabetes. Treatment with pramlintide (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 pramlintide-treated subjects achieved ≥5% weight loss vs. 2% with placebo (p<0.001). In another study with 1-year 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 pramlintide treatment in these studies **[14]**.

Also, 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 shown that topiramate has been reported to be tolerable and effective in promoting weight loss. In addition to its use in epilepsy, topiramate has received FDA approval for the prevention of migraine headaches. Topiramate has also been used offlabel 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, kidney stones, and, rarely, acute angle-closure glaucoma **[15]**.

Zonisamide is another antiepileptic drug that also reduces body weight in patients. Short-term (16 weeks) and longer-term (1 year) randomized controlled trials in patients with obesity have shown that 400 mg of zonisamide daily is effective in promoting modest weight loss (~5 kg placebo-subtracted weight). The most commonly reported adverse 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 **[16]**.

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 noradrenergic stimulation of tryptophan and serotonin by α1 and β1 adrenergic receptors on 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. An improvement in blood levels of total cholesterol and triglycerides was also observed. It was concluded that oral melatonin replacement increases the volume and activity of brown adipose tissue, as well as promoting an improvement in the lipid profile in individuals with melatonin deficiency **[17]**.

Conclusion

Some medications used off-label are gaining evidence for weight management. For example, tirzepatide is a new medication approved by the FDA in May 2022 for the treatment of type 2 diabetes mellitus and may be used off-label for the treatment of 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. AMPK2 is one of the possible targets of metformin for the treatment of obesity. Although metformin treatment in participants receiving a placebo appears to result in an initial decrease in BMI and HOMA-IR, there is no evidence of a sustained effect after long-term use in adolescents. Low-certainty evidence suggests that off-label fluoxetine may reduce weight compared with placebo. Sustained-release bupropion was more effective than placebo for weight loss when combined with a 500 kcal deficit diet. Treatment with pramlintide (up to 240 mg three times daily) for 16 weeks resulted in a placebo-corrected reduction in body weight of 3.7% and 31% of pramlintide-treated subjects achieved ≥5% weight loss vs. 2% with placebo. Oral melatonin replacement increases brown adipose tissue volume and activity, promoting thermogenesis and adipose tissue metabolism with consequent weight loss.

CRediT

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

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