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# Off-label pharmacological treatment of obesity: a systematic review of clinical studies

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## Abstract

**Introduction:** There are 2.0 billion overweight and obese people in the world, and Brazil ranks fifth in the world. The World Health Organization (WHO) advises that the use of drugs to combat obesity is indicated for patients who have a body mass index (BMI) above 30 kg/m2 or when the BMI is 25 kg/m2 associated with comorbidities. that permeate excess weight. A variety of drug classes approved for other indications have been used off-label in an attempt to promote weight loss. **Objective:** It was to list and present the main off-label drugs for obesity in adults, as well as to show the scientific evidence of clinical studies. **Methods:** The present study followed a concise systematic review (PRISMA) model. The literary search process was carried out from July 2022 to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2022. The low quality of evidence was attributed to reports of cases, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument using the Funnel Plot. **Results and Conclusion:** We found 98 studies that underwent eligibility analysis, and then 15 of the 12 total studies were selected. Most studies showed homogeneity in their results, with I2 =96.5% >50%. The Funnel Plot showed a symmetrical behavior, not suggesting a significant risk of bias in the studies. Off-label prescribing is very common among physicians who treat obesity. However, randomized controlled studies should be increasingly encouraged and increased to clearly present the scientific evidence and, thus, propose a scientific formalism for the safe and effective use of off-label anti-obesity drugs. Physicians, however, have adopted a more pragmatic approach, giving much greater credibility to shared clinical experience, particularly in situations where favorable outcomes have been consistently observed over decades. International medical bodies do not recommend the off-label use of drugs approved for the exclusive use of weight loss. In Brazil, the Brazilian Association for the Study of Obesity and Metabolic Syndrome (ABESO) recommends that drugs approved for the treatment of obesity be prescribed preferentially over off-label treatments. In addition, the patient must be well informed and aware that the drug is not approved by Anvisa for this indication or chronic use.

**Keywords:** Obesity. Pharmacological Treatment. Off-label use. Clinical studies.

## Introduction

In the obesity scenario, there are 2.0 billion overweight and obese people in the world **[1]**, and Brazil is in fifth place in the world ranking, with an estimated 18.0 million people, tending to reach 70.0 million individuals **[2]**. According to a survey carried out by the Ministry of Health, 52.5% of Brazilians are overweight, which is an important risk factor for Chronic Noncommunicable Diseases **[2]**.

After analyzing the Body Mass Index (BMI), the method of choice for the treatment of overweight BMI > 25 Kg/m2 and obesity BMI > 30 Kg/m2 should be physical activities, diets, and behavioral changes. In cases of non-significant or unsatisfactory results,

pharmacological treatment is justified [2]. The World Health Organization (WHO) advises that the use of drugs to combat obesity is indicated for patients who have a body mass index (BMI) above 30 kg/m2 or when the BMI is 25 kg/m2 associated with comorbidities that permeate excess weight [1].

In this sense, the debate about options for the pharmacological treatment of obesity continues. A variety of drug classes approved for other indications have been used off-label in an attempt to promote weight loss [2-8]. Off-label use is defined by ANVISA as "the use in situations different from the package insert of a drug registered with ANVISA. It may include differences in indication, age/weight range, dose, frequency, presentation or route of administration" [2]. Among these drugs, anticonvulsants such as topiramate, drugs used to control diabetes such as metformin, antidepressants such as fluoxetine and bupropion, and the hormone melatonin stand out.

Thus, prescribing drugs for off-label use is not illegal, however, using a drug outside the recommended dosage range or duration of use can put patients' health at risk, given that there is no scientific formalism for this [3,9-12]. Thus, drugs would be considered appropriate for off-label use, based on their known clinical pharmacology and scientific evidence from clinical studies [13-15]. The decision to use an off-label drug should be based on a careful assessment of the patient's treatment history and the potential risks and benefits of the drug.

Patients should receive adequate informed consent about how the drug is being used off-label and why along with appropriate information about known risks and side effects [3]. In the last 20 years, the US Food and Drug Administration (FDA) has approved 9 drugs for the treatment of obesity. Phentermine is FDA-approved for shortterm use only and is used off-label for the long term [4]. Therefore, the present study aimed to list and present the main off-label drugs for obesity in adults, as well as to show the scientific evidence from clinical studies.

## Methods

### Study Design

The rules of a systematic review of the PRISMA platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

### Data Sources and Research Strategy

The literary search process was carried out from July to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2022, using the descriptors (MeSH Terms): Obesity. Pharmacological Treatment. Off-label use. Clinical studies, and using the Booleans "and" between the descriptors (MeSH Terms) and "or" between the historical findings.

### Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. 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 through the analysis of the Funnel Plot (Cohen test (d)).

## Results and discussion

### Summary of Literary Findings

A total of 98 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 44 articles. A total of 15 articles were fully evaluated and 12 were included and developed in the present systematic review study **(Figure 1)**. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 32 studies at high risk of bias and 43 studies that did not meet the GRADE. Most studies showed homogeneity in their results, with I2 =96.5% >50%.

**Figure 1.** Flowchart showing the article selection process.

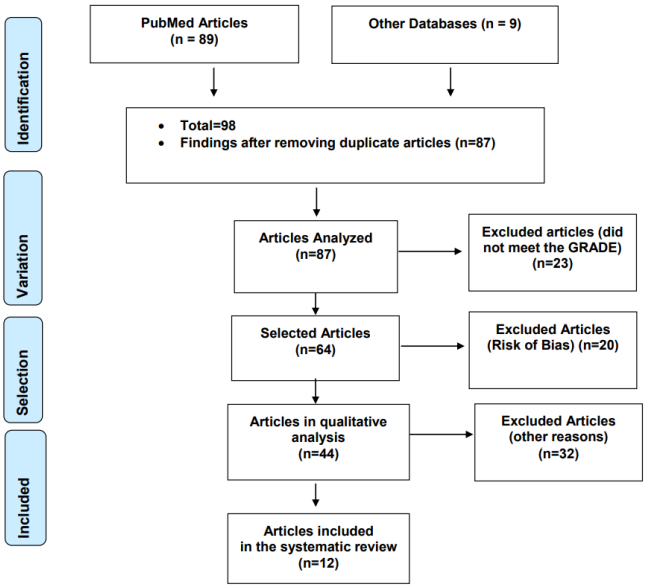
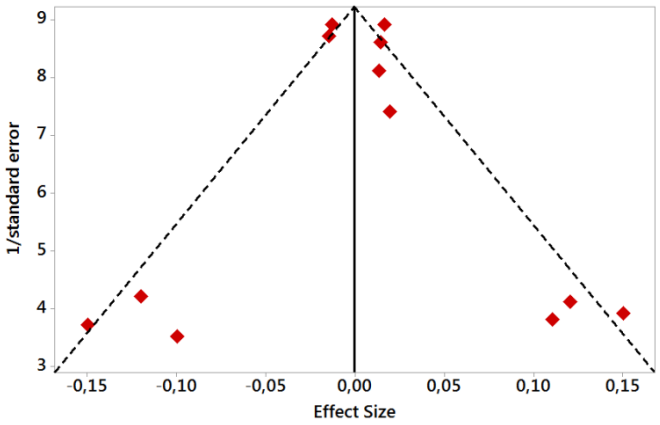


**Figure 2** presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error. This graph showed symmetrical behavior, not suggesting a significant risk of bias, both between 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 presented in the upper region.

**Figure 2.** The symmetrical funnel plot suggests no risk of bias between the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (NTotal=12 studies evaluated in full in the systematic review).




## Major Off-label Anti-obesity Drugs

It is worth noting that the longer a drug has been in use, the greater the probability of knowing its safety and efficacy which were not contemplated before or even during the approval process. Long-term use may demonstrate that the initial safety label warnings are unfounded. Therefore, the information contained in the package inserts of older drugs may be out of date due to the unavailability of more recent clinical research and proven scientific evidence.

**Table 1**. below presents the main anti-obesity drugs used off-label and, soon after, in the next section, the main clinical studies regarding the safety and efficacy of some of the off-label anti-obesity drugs were presented.

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

| Drugs Off Label | Prescription | Dose Anti-Obesity | Biases |
|---|---|---|---|
| Fluoxetine [5] | - Serotonergic agent;<br>- Antidepressant; | 60 mg | - Dose-related effect on weight loss.<br>- Help with short-term weight reduction; |
| Duloxetine [5] | - Treatments for major depressive disorders, painful diabetic neuropathy and urinary incontinence | | -Despite significantly reducing food intake, scientific evidence from randomized studies is still lacking. |
| Lisdexanfetamine [6] | - Dextroamphetamine prodrug,<br>-Promotes the release of monoamine neurotransmitters. | 50 mg or 70 mg diary | - Safety and efficacy are not established for the treatment of obesity. |
| Phentermine [6] (Long-term) | - Long-term off-labell.<br>-Amphetamine derivative.<br>- Appetite suppressant | | -Its potential long-term adverse effects are not proven |
| Metformin [8] | Type 2 diabetes treatment | 850 mg three times a day (2,550 mg/day) | -While not an approved indication, evidence indicates efficacy.<br>- There are also studies with metformin to treat antipsychotic treatment-induced weight gain. |
| Topiramate [13] | -Epilepsy; Lennox-Gastout Syndrome;<br>- Migraine | 64 mg to 384 mg | -Although the exact mechanism of its action in the management of weight loss is not known, Topiramate has been tested as an adjunct to treat obesity and appears to be reasonably well tolerated. |
| Bupropion [11] | -Selective inhibitor of dopamine and, to a lesser extent, of norepinephrine.<br>-Treatment of depression and | 300 mg/day to 600 mg/day | -Clinical studies show that bupropion can cause both weight loss and weight gain, |

| | | | |
|---|---|---|---|
| | nicotine addiction. | | although with different incidences. |
| Semaglutide [5] | -Is used, in conjunction with diet and exercise, to treat adult patients with unsatisfactorily controlled type 2 diabetes | 4 mg in 3 mL. | -Although it has shown a slimming effect, clinical studies were carried out only with diabetic patients. |
| Exenatide [4] | -Treatment of diabetes | De 5 to 10 mcg, 2 times per day | - Safety and efficacy are not established for the treatment of obesity. |
| Zonisamide [14] | - 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 are not established for the treatment of obesity. |
| Pramlinitide [12] | -Treatment of diabetes. | 120 mcg | -Although it can promote weight loss in non-diabetic patients, there is still no scientific evidence of its effectiveness. |
| Metreleptin [4] | - Approved for congenital or acquired generalized lipodystrophy. - Metreleptin is a synthetic analogue of leptin. | 10 mg (2 mL) | - Administration of leptin after weight loss in obese patients may reverse some of the neuroendocrine adaptations involved in weight regain. However, studies are scarce. |
| Melatonin [15] | - Sleep disorders. | 1 to 10 mg | - Scarce clinical studies. |

## Major Clinical Studies

The first clinical trial on the effect of metformin was conducted in the US 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 inhibiting gluconeogenesis alongside a weight loss effect involving adipose tissue. Then another 27-center randomized clinical trial 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 through activation of activated AMP protein kinase subunit 2 (AMPK2) in the skeletal muscle of rats. Importantly, a study conducted from 2009 to 2013 to assess 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 drug to reduce weight in 154 non-diabetic outpatients with a body mass index greater than 27 kg/m2 **[7]**.

After that, a randomized clinical trial for six months concluded that metformin 1000mg twice daily is useful in treating obesity. Also, several form studies 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 cellular energy balance by directly controlling 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 insulin resistance through the elevation of fatty acids. Clinically, AMPK2 is the critical regulator of cell-consuming operations, triggering the catabolic pathways out of ATP. Therefore, it appears that AMPK2 is one of the possible targets of metformin for the treatment of obesity. However, one question remains unanswered regarding the possibility of metformin targeting CDK4 in normal obese patients to produce its major pathway through adipose tissue **[7]**.

The use of metformin in the treatment of obesity is very common. However, studies on long-term treatment with metformin in obese patients are scarce. Therefore, an 18-month open-label extension study was conducted following an 18-month randomized placebo-controlled trial (RPC) on the efficacy, safety, and tolerability of metformin in adolescents with obesity and insulin resistance. Upon completion of the RPC, metformin was offered to all participants with a body mass index (BMI-SDS) standard deviation score > 2.3 and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) ≥ 3,4. The endpoints were changed in the 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 who continued on metformin, an increase in BMI (+2.2) and HOMA-IR (+13.7) was observed. In participants who received a placebo, BMI stabilized after an initial decrease (+0.5). For HOMA-IR, a decrease (-1.1) was observed. Although treatment with metformin in participants who received 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. Limited adherence and/or the insufficient dose may explain differences in long-term effects between adolescents and adults **[8]**.

Fluoxetine is a serotonin reuptake inhibitor indicated for major depression. This is also thought to affect weight control, through changes in appetite, resulting in lower food intake and normalization of unusual eating behaviors. However, the benefit-risk balance of this off-label drug is unclear. Thus, one study evaluated the effects of fluoxetine in overweight or obese adults. Randomized clinical trials comparing the administration of fluoxetine versus placebo, other anti-obesity agents, nonpharmacological therapy, or no treatment in overweight or obese adults without depression, mental illness, or abnormal eating patterns were included. Trials were evaluated for overall certainty of evidence using the GRADE instrument. Random effects meta-analyses were performed and the hazard ratio (HR) was calculated with 95% confidence intervals (95%CI) for dichotomous outcomes and the mean difference (MD) with 95%CI for continuous outcomes. We identified 1036 records, analyzed 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- hydroxy-tryptophan; no treatment; and omega-3 gel). Within the 19 randomized trials, there were 56 trial arms. Fifteen clinical trials were performed in parallel randomized clinical trials and four in randomized crossover 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 **[9]**.

Thus, in that study, comparing fluoxetine versus placebo, at all fluoxetine dosages and durations of treatment, DM was -2.7 kg (95% CI -4 to -1.4; $p < 0.001$; 10 trials, 956 participants; low-certainty evidence). The 95% prediction range ranged from -7.1 kg to 1.7 kg. The DM in body mass index (BMI) reduction at all doses of fluoxetine compared to placebo was -1.1 kg/m$^2$ (95% CI -3.7 to 1.4; 3 trials, 97 participants; evidence of very low certainty). Only nine placebo-controlled studies reported adverse events. A total of 399 of 627 participants (63.6%) who received fluoxetine compared with 352 of 626 participants (56.2%) who received a placebo experienced an adverse event. Random effects meta-analysis showed an increased risk of having at least one adverse event of any type in the fluoxetine groups compared with placebo (HR 1.18, 95% CI 0.99 to 1.42; p=0 .07; 9 studies, 1253 participants; low-certainty evidence). The 95% prediction interval ranged between 0.74 and 1.88 **[9]**.

Also in that study, after treatment with fluoxetine, adverse events of dizziness, drowsiness, fatigue, insomnia, and nausea were observed approximately twice as often as placebo. A total of 15 of 197 participants (7.6%) who received fluoxetine compared with 12 of 196 participants (6.1%) who received the placebo experienced depression. The HR at all doses of fluoxetine compared to 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 effects were not reported. Comparisons of fluoxetine with other anti-obesity agents (3 trials, 234 participants), omega-3 gel (1 trial, 48 participants), and no treatment (1 study, 60 participants) showed inconclusive results (very low certainty evidence). Therefore, low-certainty evidence suggests that off-label fluoxetine may decrease weight compared to a placebo. However, low-certainty evidence suggests an increased risk of dizziness, drowsiness, fatigue, insomnia, and nausea after fluoxetine treatment **[9]**.

Patients with type 1 diabetes often have suboptimal glycemic control. The gold standard of treatment is basal-bolus insulin or subcutaneous infusion of insulin 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 has historically been called type 1 and type 2 diabetes. Thus, one study looked at the use of antihyperglycemic agents that target other pathophysiological abnormalities. to facilitate weight loss and improve glycemic control. A MEDLINE search was performed from 1975 to October 2018 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 25kg/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 **[10]**.

Bupropion is an atypical antidepressant that unduly causes weight loss. Although the average weight loss seen with bupropion is small, as an antidepressant it is preferable to many drugs that can induce weight gain. Anderson et al. **[11]** 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 percent loss from baseline body weight for subjects completing 24 weeks were 5.0%, 7.2%, and 10.1% for placebo, sustained-release bupropion 300, and 400 mg/d, respectively. In obese subjects 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 FDA-approved injectable agent for the treatment of type 1 and types 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 pooled posthoc analysis of overweight and obese insulin-treated patients with type 2 diabetes, pramlintide-treated patients (receiving 120 mg twice daily) had a reduction in body weight of -1.8 kg (p< 0.0001) compared to placebo-treated patients. In this study, patients treated with pramlintide had a 3-fold increase in successfully achieving >5% total body weight loss compared to those receiving placebo. Subsequently, randomized trials combining pramlintide or placebo with a lifestyle intervention were performed 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% loss. of weight vs. 2% with placebo (p< 0.001). In another study with a one-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 is the most common adverse event with pramlintide treatment in these studies **[12]**.

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 studies have shown that topiramate has been reported to be tolerable and effective in promoting weight loss. In addition, to 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 usually seen with other antiepileptic agents. Topiramate can cause paresthesia, cognitive side effects, as well as kidney stones, and, rarely, acute-angle glaucoma **[13]**.

Zonisamide is another antiepileptic drug that also reduces body weight in patients. Short (16 weeks) and longer (one year) randomized controlled trials in obese patients have shown that 400 mg of zonisamide daily is effective in promoting modest weight loss (~5 kg weight subtracted by placebo). 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 who are hypersensitive to sulfonamides **[14]**.

Melatonin is a hormone produced mainly 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 $\alpha 1$ and $\beta 1$ 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 the volume and activity of brown adipose tissue measured by positron emission tomography. Improvement in blood levels of total cholesterol and triglycerides was also observed. It is concluded that oral melatonin replacement increases the volume and activity of brown adipose tissue, as well as promotes the improvement of the lipid profile in individuals with melatonin deficiency **[15]**.

## Conclusion

Off-label prescribing is very common among physicians who treat obesity. However, randomized controlled studies should be increasingly encouraged and increased to clearly present the scientific evidence and, thus, propose a scientific formalism for the safe and effective use of off-label anti-obesity drugs. Physicians, however, have adopted a more pragmatic approach,

giving much greater credibility to shared clinical experience, particularly in situations where favorable outcomes have been consistently observed over decades. International medical bodies do not recommend the off-label use of drugs approved for the exclusive use of weight loss. In Brazil, the Brazilian Association for the Study of Obesity and Metabolic Syndrome (ABESO) recommends that drugs approved for the treatment of obesity be prescribed preferentially over off-label treatments. In addition, the patient must be well informed and aware that the drug is not approved by Anvisa for this indication or chronic use.

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## Conflict of interest
The authors declare no conflict of interest.

## Similarity check
It was applied by Ithenticate@.



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