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REVIEW ARTICLE

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Main considerations of off-label drugs in patients with excessive adipose tissue and obesity: a systematic review

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Abstract

Introduction: The rise of the obesity pandemic has been underestimated since most assessments do not include perhaps up to 2.7 billion patients with excessive stores of adipose tissue and calories. A variety of classes of anti-obesity drugs approved for other indications have been used off-label in attempts to promote weight loss. **Objective:** It was to discuss the main off-label drugs for treating excess fatty tissue and obesity through clinical studies and consensus among world societies. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from September to October 2023 in the Web of Science, Scopus, 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 115 articles were found, 30 articles were evaluated in full, and 22 were included and developed in the present systematic review study, out of a total of 24 (2 references are on the website and were not included) Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 18 studies with high risk of bias and 27 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=58.6%>50%. It was concluded that the current paradigm for the diagnosis and treatment of obesity is for those with high BMI, however, the paradigm is flawed for patients with lower BMI in the early stages of abnormal adipose tissue accumulation, who are often ignored and left without treatment. This promotes the continuation of obesity worldwide, allowing early-stage patients to accumulate increasingly greater amounts of adipose tissue. Thus, the use of off-label antiobesity drugs has accumulated scientific evidence for a safe and effective treatment. However, it is still necessary to promote more observational studies and medical reports to corroborate the findings so far present in randomized studies.

Keywords: Obesity. Off-label drugs. Excess adiposity. Weight loss.

Introduction

The rise of the obesity pandemic has been underestimated, as most assessments fail to include

perhaps as many as 2.7 billion patients with excess adipose tissue and calorie stores **[1]**. These energy-excess patients are not classified as overweight or obese. Significant progress has been made in understanding the pathophysiological processes involved in excess adiposity. Adipose tissue is a dynamic organ and metabolically active in the production of hormones, which release a storm of molecules that incite multifaceted systemic inflammatory processes **[1,2]**.

Lifestyle modification is an important component of comprehensive obesity treatment. One facet of this treatment is the improvement and reduction of harmful eating behaviors. Appetite regulation has long been a focus of the effects of anti-obesity medications, but there is now also evidence that some anti-obesity medications induce beneficial changes in eating behavior **[4]**. These observations suggest that short- and longterm pharmacotherapy of obesity may be an essential adjunct to behavior modification therapy **[5]**. In this scenario, a variety of classes of drugs approved for other indications have been used off-label in an attempt to promote weight loss **[5]**.

Among these drugs, the most notable are anticonvulsants, such as topiramate, drugs used to control diabetes, such as metformin, antidepressants, such as fluoxetine and bupropion, naltrexone (treatment of opioid dependence and alcoholism), tirzepatide, the hormone melatonin, etc. **[4-8]**. In this sense, 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. The paradigm is centered on BMI, restricting pharmacotherapy to patients with a BMI equal to or greater than 30 kg/m2 or 27 kg/m^2 in the presence of a disease associated with excess adiposity, such as diabetes. Great emphasis in treatment is placed on lifestyle modification, and pharmacotherapy is considered an adjunctive treatment modality to behavior modification. No emphasis is placed on the treatment of patients with excess adiposity **[9]**.

Therefore, this systematic review study discussed the main off-label drugs for treating excess fatty tissue and obesity through clinical studies and consensus of world societies.

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: 09/27/2023. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 09/27/2023.

Data Sources and Search Strategy

The literature search process was carried out from September to October 2023 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following Health Science Descriptors (DeCS/MeSH Terms) were used: "Obesity. Off-label drugs. Excess adiposity. Weight loss", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

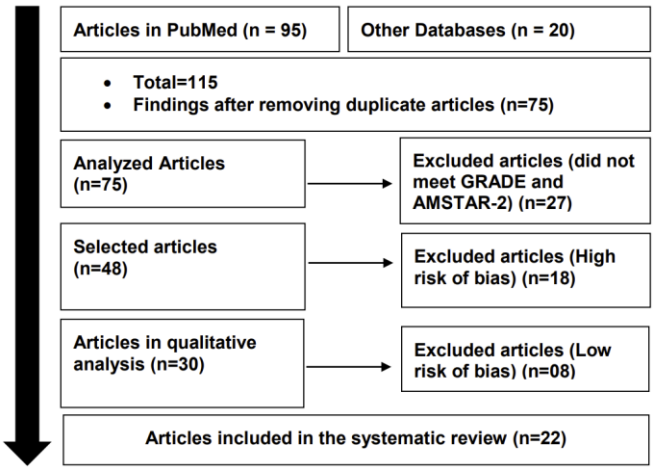
Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low 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 115 articles were found that were submitted to eligibility analysis, and 22 final studies were selected to compose the results of this systematic review, out of a total of 24 (2 references are websites that were not included in the risk of bias analysis). The listed studies were of 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=58.6%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 27 studies that did not meet GRADE and AMSTAR-2.

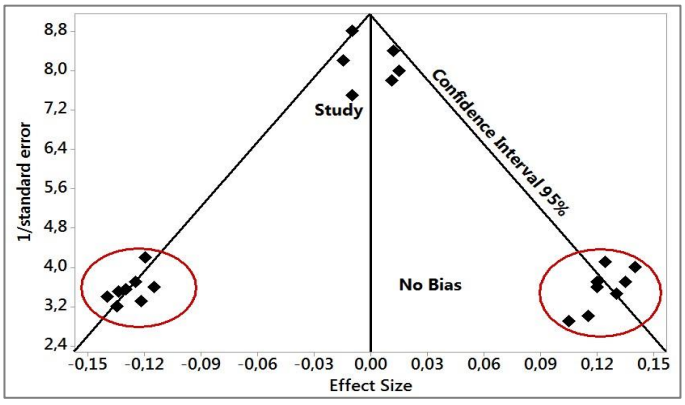
Figure 1. Selection of articles by exclusion based on GRADE and AMSTAR-2.



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 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 size (lower precision) that are shown at the base of the graph and in studies with large sample size that are presented at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample size that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n = 22 studies).



Source: Own Authorship

Off-Label Anti-Obesity Drugs

Treatment of excess adiposity still focuses on the late stages. BMI values are not sensitive enough to identify patients in the early stages of pathological adipose tissue accumulation. Even modest amounts of fat accumulation have adverse health implications and, if left untreated, are associated with increased mortality rates **[10]**. Although the notion of metabolically healthy obesity persists, these reports often ignore the trajectory of the disease and fail to recognize that being healthy is often a transient state in an obese patient **[11-13]**.

In this context, off-label prescribing is all too common. The Food and Drug Administration (FDA) and academic physicians insist that only evidence from randomized controlled trials should be trusted and denigrate clinical experience and observational studies. Physicians have adopted a more pragmatic approach, giving much more credence to shared clinical experience, particularly in situations where favorable outcomes have been consistently observed over decades **[10,11]**.

Furthermore, clinicians pay more attention to excess fat stores as an indicator of disease and less attention to BMI thresholds, particularly for those with excess fat with BMI below thresholds. Many believe that BMI is too insensitive for diagnosis and that the use of BMI fails to identify patients who would be best served by early treatment. Thus, naming the disease as obesity has hampered patient care in the early stages **[10,11]**.

In this sense, the drug tirzepatide 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. The starting dose is 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. However, clinical studies have accumulated evidence of the off-label action of this drug for weight loss in obese patients **[14-16]**.

Also, bupropion combined with naltrexone is approved for use in the US, but in Brazil, the medications can be prescribed separately. Bupropion acts on adrenergic and dopaminergic receptors in the hypothalamus, and naltrexone is an opioid receptor antagonist. Bupropion is indicated in the package insert for treating smoking, depression, and anxiety. Naltrexone, on the other hand, is originally used to treat alcoholism and neutralize 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, up to 5% more weight loss than in the placebo group. The most common adverse reactions are nausea, constipation, headache, vomiting, and dizziness **[17,18]**.

Binge eating disorder, the most prevalent eating disorder, is a serious public health problem associated with obesity. Authors Grilo et al. (2022) conducted a randomized, double-blind, placebo-controlled study to analyze the efficacy of naltrexone-bupropion and behavioral therapy for weight loss (PP), alone and in combination, for binge eating disorders comorbid with obesity. A total of 136 patients with binge eating disorder (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), PP+placebo (N=35), or PP+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) **[19]**.

Additionally, tirzepatide is the first dual GLP-1/GIP receptor co-agonist approved for the treatment of 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. Overtreatment 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 analogues **[20]**.

A six-month randomized clinical trial concluded that metformin 1000 mg twice daily is useful in the treatment of obesity. In addition, several studies have illustrated the mechanism of action of metformin in obesity. However, the major pathway of metformin that induces weight loss is through the loss of adipose tissue in conjunction with the regulation of energy expenditure with exercise. In this context, cyclin-dependent kinase 4 (CDK4), a protein involved in cell division, organizes cellular energy balance through direct control of 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 that contributes to the development of obesity-related to insulin resistance through elevated fatty acids.

Clinically, AMPK2 is the critical regulator of cellular consumption operations, 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, a question remains unanswered regarding the possibility of metformin targeting CDK4 in normal obese patients to produce its major pathway via adipose tissue **[21]**.

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 together with insulin regulates postprandial glucose control. Its effect on weight loss is thought to be mediated by central (brain) receptors that enhance 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 reduction in body weight of -1.8 kg ($p<0.0001$) compared with placebo-treated patients. In this study, patients treated with pramlintide had a 3-fold increase in successfully achieving a total body weight loss of >5% when 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 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 pramlintide treatment in these studies **[22]**.

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 side

effects compared with placebo were gastrointestinal (nausea/vomiting), nervous system (headaches), and cognitive (anxiety, impaired memory, language problems). Zonisamide should not be given to patients hypersensitive to sulfonamides **[23]**.

Finally, melatonin is a hormone produced mainly by the pineal gland, but also in the gastrointestinal tract, retina, lacrimal glands, skin, erythrocytes, platelets, lymphocytes, and mononuclear cells of the bone marrow, 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 the volume and activity of brown adipose tissue measured by positron emission tomography. An 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 improvement in the lipid profile in individuals with melatonin deficiency **[24]**.

Conclusion

It was concluded that the current paradigm for the diagnosis and treatment of obesity is for those with high BMI, however, the paradigm is flawed for patients with lower BMI in the early stages of abnormal adipose tissue accumulation, who are often ignored and left untreated. This promotes the continuation of obesity worldwide, allowing early-stage patients to accumulate ever-increasing amounts of adipose tissue. Thus, the use of off-label anti-obesity drugs has accumulated scientific evidence for a safe and effective treatment, but more observational and clinical-report studies are still needed to corroborate the findings presented so far by randomized trials.

CRediT

Author contributions: **Conceptualization -** Rodrigo Siqueira de Carvalho, Mariana Carolina Braga; **Data curation -** Alessandra Leal de Oliveira, Thuany da Silva Teixeira, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro; **Formal Analysis -** Rodrigo Siqueira de Carvalho, Mariana Carolina Braga, Alessandra Leal de Oliveira; **Investigation -** Rodrigo Siqueira de Carvalho, Mariana Carolina Braga, Alessandra Leal de Oliveira, Thuany da Silva Teixeira, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro; **Methodology -** Thuany da Silva Teixeira, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro; **Project administration -** Rodrigo Siqueira de Carvalho; **Supervision -** Rodrigo Siqueira de Carvalho; **Writing - original draft -** Rodrigo Siqueira de Carvalho, Mariana Carolina Braga, Alessandra Leal de Oliveira, Thuany da Silva Teixeira, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro; **Writing-review & editing-** Rodrigo Siqueira de Carvalho, Mariana Carolina Braga, Alessandra Leal de Oliveira, Thuany da Silva Teixeira, Lucas Emanuel de Lima Azevedo, Lara Souza Crepaldi, Renata Cristina Taveira Azevedo, Nathalia Galindo Cordeiro.

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Informed Consent

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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[@].

Peer Review Process

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