BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902025e24177

Review

Medicines for the management of overweight and obesity: A systematic review with network meta-analysis

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To synthesize the evidence about pharmacologic treatment of obesity and overweight and to define the options with the best risk-benefit using the stochastic analysis of multicriteria acceptability (SMAA). The analysis addresses a systematic review (PROSPERO CRD42023423308) whose research was realized in PubMed, Scopus, and Web of Science. Randomized controlled trials were included, which verified the effects of sibutramine, orlistat, liraglutide, and semaglutide in patients with IMC ≥ 26 Kg/m². The risk of bias analysis was performed with RoB 2.0 and the outcomes evaluated were weight loss and serious adverse events. A total of 102 studies with 45.047 participants were included. The network meta-analysis revealed that all the treatments were significantly more effective than the placebo in weight reduction. The use of semaglutide (especially 0.4 mg/day) was associated with a bigger weight loss in comparison to all the other treatments ($p<0.05$) and the analysis of SMAA showed a risk-benefit of 95%. Besides that, we suggest re-evaluating of sibutramine 10mg/day as a therapeutic option for patients without hypertension or cardiovascular diseases, and we demonstrate the modest weight loss promoted by orlistat 120mg, sibutramine 5mg, and liraglutide 1,8mg and advise against its use, once the benefits do not outweigh the risks.

Keywords: Weight loss. Adverse events. Risk-benefit. Pharmacological treatment. Obesity.

INTRODUCTION

The incidence of obesity has been growing over the last decades, covering approximately one-third of the population, and affecting men and women of all ages. This public health problem had a sharp increase during the COVID-19 pandemic, due to unhealthy eating behaviors, the growth of physical inactivity, and the significant limitation to access to health services (Bentham, 2017; Melamed, Selby, Taylor, 2022; Lobstein *et al.*, 2023).

The number of individuals with obesity or who are overweight was 2.6 billion in 2020, with an estimate to overtake the number of 4 billion by the year 2035. Such data demonstrates a rise of more than 50% in the cases of overweight and 24% in the cases of obesity (Lobstein *et al.*, 2023).

Obesity predisposes the development of a series of comorbidities such as diabetes mellitus, cardiovascular diseases, cancer, and sleep apnea, among others. Besides those medical implications, this disease also has significant effects on the individual's life quality, causing damage to

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their mobility, self-esteem, productivity in their workplace, and participation in social activities. This situation corroborates social isolation, which can drastically affect the individuals' mental health and even cause premature death (Lobstein *et al.*, 2023; Blüher, 2019; Lin, Li, 2021).

Furthermore, this clinical condition has an extremely elevated budgetary impact that might reach 4 trillion dollars by 2035 globally. These figures include costs arising from obesity and overweight treatments and their consequences, as well as factors related to the reduction of productivity and job abstention (Okunogbe *et al.*, 2022). Considering all of these factors, the existence of high-quality studies which compare directly and indirectly the multiple therapeutic alternatives available is of paramount importance, enabling each time more assertive decision-making based on robust evidence.

The obesity treatment is based on two essential pillars, changes in lifestyle that should include a well-balanced diet and regular physical activity, and pharmacological interventions that include the use of medications. In some cases, surgical interventions such as bariatric surgery are necessary (Brazilian Association for the Study of Obesity, 2016; Grunvald *et al.*, 2022; NHLBI Obesity Education, 2023). The list of medicines recommended for weight reduction includes the analogs of GLP-1, liraglutide and semaglutide, the inhibitor of gastrointestinal lipase, orlistat, and the inhibitor of the reuptake of serotonin and norepinephrine, sibutramine. All the medications mentioned above are approved for this purpose by the Food and Drug Administration (FDA) (2022) and European Medicines Agency (EMA) (2023), sibutramine the exception which is only allowed by the National Agency of Sanitary Vigilance (ANVISA) (Grunvald *et al.*, 2022; NHLBI Obesity Education, 2023; National Health Surveillance Agency, 2014).

Many systematic reviews and meta-analyses have been published over the last years about the pharmacological treatment of obesity, but most of them do not include sibutramine - as it is not approved for use in several countries. Moreover, studies often fail to provide dosage-level results and lack of thoroughly assessing the certainty of evidence, which can make it challenging for clinicians and researchers to make informed decisions about treatment protocols or recommendations (Iannone *et al.*, 2023; Smith *et al.*, 2022; Xie *et al.*, 2022). An extensive systematic review conducted by Iranian researchers evaluated all the pharmacological options (approved and discontinued) for obesity, where it has shown that sibutramine associated with lifestyle changes was the second-best option for weight loss among adults of both sexes, only coming after semaglutide. (Morsali *et al.*, 2023).

A systematic review of randomized and controlled trials with 49.820 adult participants evaluated medicines approved by the American Guidelines of Obesity, that demonstrated the effectiveness and security of medications such as semaglutide and liraglutide and highlighted the lack of benefits of orlistat for weight control (Shi *et al.*, 2022), however, it is relevant to include sibutramine on those analyses to determine if it should prevail in the therapeutic arsenal of obesity

The network meta-analysis allows the performance of comparative studies between different interventions, directly or indirectly, knowing that it is not always possible to conduct primary studies with so many different medicines (Higgins *et al.*, 2023). Besides that, we have chosen to accomplish a stochastic analysis of multicriteria acceptability, which allowed us to evaluate which the best and worst options of treatment for different health issues (Domingos *et al.*, 2022; Madeira *et al.*, 2021; Chai *et al.*, 2023; Tonin *et al.*, 2017). We have not found any studies that evaluate medicines for weight loss making use of this analysis, which can facilitate the decision-making of the prescribers and the update of the guidelines about the pharmacological treatment of obesity.

Therefore, given these gaps in the literature, we synthesized the available evidence about the pharmacological treatment of obesity (sibutramine, orlistat, liraglutide, and semaglutide) in any age group through a large systematic review with network meta-analysis and stochastic analysis of multicriteria acceptability.

MATERIAL E METHODS

This study was performed in accordance with the recommendations of the Cochrane Collaboration and reported following the guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), PRISMA extension for Network Meta-Analyses (PRISMA-NMA) (Higgins *et al.*, 2023; Page *et al.*, 2021; Hutton *et al.*, 2015). Two authors independently conducted all steps of study selection and data extraction, in cases of discrepancies, a third reviewer was consulted. The protocol is available at PROSPERO (CRD42023423308).

Search strategy and eligibility criteria

The strategic search was carried out in the databases PubMed, Scopus, and Web of Science, without time or language restrictions (search updates in May 2023). The clinical trial registry databases and reference lists of included studies were also manually searched. The full search strategy is available in the Supplementary Material.

The titles and abstracts of the retrieved records were selected for eligibility and those that were relevant for this review were, then, read in full. Primary studies that met the following criteria (PICOS' acronym) were included for the extraction and data analysis: (i) studies including overweight or obese individuals (defined as those with BMI $\geq$ 26 Kg/m²) in any age (with or without comorbidities); (ii) evaluate the effects of anti-obesity medicines (sibutramine, orlistat, liraglutide, or semaglutide) at any dose (combined or not with co-interventions like diet and exercises); (iii) comparison to any other pharmacological intervention or placebo/usual care as control; (iv) provision of data on clinical outcomes (at least one of the following: weight loss, serious adverse events); (v) designed as randomized controlled trials.

Open-label clinical trials, cross-sectional studies, articles that evaluated only economic or quality of life outcomes, unavailable studies or registers with no data for extraction, and articles in non-Roman characters were excluded.

Data extraction and methodological quality assessment

A standardized form was used to extract information on general data from the articles (authors, year of publication, country, and sample size); study design; characteristics of participants (age, sex); intervention and controls (medicines, diet); clinical outcome results and measurement times (Microsoft Excel, Redmond, WA). The methodological quality of the included studies was assessed using the Cochrane Collaboration tool to assess the risk of bias in randomized trials (RoB 2.0) (Higgins *et al.*, 2019) which incorporates the evaluation of different sources of bias (selection, performance, detection, attrition, and reporting bias) by comparison of results. Evidence is judged to have a low risk of bias, some concerns, or a high risk of bias.

Summary of information and statistical analyses

A narrative synthesis of the included studies was elaborated, and structured around the intervention, target population, and results, provided in tables. Network meta-analyses (multiple or mixed treatment comparisons) were conducted for each outcome of interest, as recommended by the International Society for Pharmacoeconomics and Outcomes Research (Hoaglin *et al.*, 2011; Jansen *et al.*, 2011). We used random effect models based on the Markov Chain Monte Carlo (MCMC) simulation method to obtain clustered effect sizes (burn-in: 20.000 iterations; 50.000 iterations for estimation) (Dias *et al.*, 2013; Lu, Ades, 2004). Transitivity analyses were performed by

comparing the population, interactions, comparator, and outcome definitions between studies. A conservative non-informative background check was employed. The level of complexity of primary studies (i.e., arm-level input data) was found in the network geometry to be consistent with the treatment arms provided by the trials. A standard heterogeneity parameter was assumed for all comparisons. The relative effect sizes of the treatments have been reported as odds ratio (OR) with 95% Credibility Intervals (CI). The effect models (fixed or random models) were selected according to the information criteria of lower deviation. Convergence was obtained based on visual inspection of the Brooks-Gelman-Rubin plots and the potential downscaling factor (PSRF) ($1<PSRF\leq1.05$). Classification probabilities involving all treatment options, aiming to increase the estimated accuracy of the relative effect sizes of the comparisons were constructed for each outcome. In order to better represent the results of the classification, the surface under the cumulative rating curve was calculated (SUCRA) (Jansen *et al.*, 2011; Mbuagbaw *et al.*, 2017). Node split analyses were performed as part of the network inconsistency assessment ($p<0.05$ values reveal significant inconsistencies between the direct and indirect evidence gathered for a specific comparison) (Veroniki, Higgins, Salanti, 2013; Tonin *et al.*, 2019).

Network meta-analyses were performed on Addis v.1.16.6 (Aggregate Data Drug Information System; // drugis.org/index) and confirmed on R/RStudio (pacote gemtc). The network graphics were built on Gephi 0.9 (https://gephi.org).

Multicriteria Analysis

Stochastic multicriteria acceptability analysis (SMAA), an extension of Multicriteria Decision Analysis (MCDA), was also performed with the main goal of estimating the risk-benefit relationship between the interventions. 'Benefit' is defined as the effect that takes the patient from the disease condition to health/cure, while 'risk' describes an effect that leads from health to disease. This model simultaneously evaluates different attributes of therapeutic efficacy and safety and provides a classification of the treatments (from the worst to the best clinical option), which is useful for the process of decision-taking (Tervonen *et al.*, 2011; Chisholm, Sharry, Phillips, 2022; Frazão *et al.*, 2018).

The SMAA models were built using evidence from a network meta-analysis of clinical trials about anti-obesity therapies with unknown or partially unknown preferences. A benefit criterion (weight loss) and a risk criterion (serious adverse event) were considered. A model with missing preferences (i.e., without a previously established order of importance for these results) was constructed to provide a brief overview of the evidence. In the following step, as part of the sensitivity analyses, additional models were developed considering the preferred order in which the results would occur. In the main scenario (scenario I), orlistat 120 mg/3x day was considered the basic treatment for being the most commonly used drug in the daily practice of these patients. An alternative scenario was also built (scenario II) using a placebo as a baseline comparator. The models were created using iterations of the MCMC (Addis v.1.16.6 - Aggregate Data Drug Information System; //drugis.org/index).

Assessing the certainty of evidence

The certainty of the evidence at the outcome level (weight loss and incidence of serious adverse events) was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group tool (GRADEpro) (Schünemann *et al.*, 2013; GRADEpro GDT, 2024). Outcomes for a given comparison were classified as having high, moderate, low, or very low quality based on five main criteria (risk of bias, imprecision, indirectness, heterogeneity, publication bias). The main comparator was fixed as a placebo (Brazil, 2015).

RESULTS

The search strategy retrieved 1.225 records after removing duplicates, of which 1.054 were deemed irrelevant during screening (title reading and summaries). Sixty-nine registers were excluded after evaluating the

complete text (see the full list of excluded studies with grounds for exclusion in supplementary material), leaving 102 trials for data extraction and analysis (see Figure 1).

Those 102 trials (n = 45.047 patients; ages between 7 and 80 years old) were published between 1995 and 2022, in more than 20 different countries, being conducted mainly in the United States of America (n=34; 33.3%), followed by Brazil and Mexico (n=7 each; 6.8%) and in some other European countries such as Germany, Italy, and Denmark (n=6 each, 5.9%). In general, 40 studies (39.2%) evaluated the effects of sibutramine (5, 10, 15, or 20 mg/day), while orlistat (60 or 120 mg/3x day) was evaluated on 33 trials (32.4%) and liraglutide (1.8 or 3 mg/day) on 22 studies (21.6%). Only six trials (5.9%) used semaglutide (0.4 mg/day or 2.4 1.7 or 1 mg/week). Most studies (n=101; 99%) compared the active medication to the placebo. The duration of the trial follow-up ranged from 5 to 208 weeks. See the characteristics of the studies in the supplementary material.

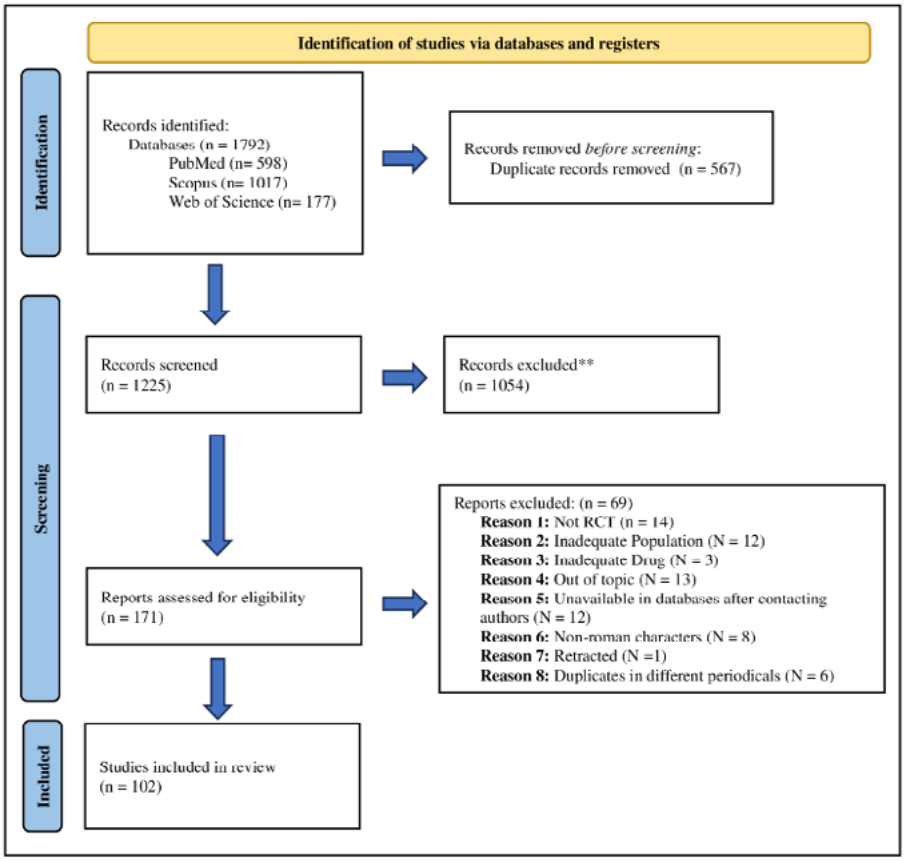

FIGURE 1 – Flow diagram of the systematic review.

The methodological quality of the trials included was evaluated according to the results of weight loss and serious adverse events (n = 204). From those, 42 (20.6%) results had shown a high bias risk, and 115 (56.4%) were considered concerning (see complete evaluation in supplementary material). Trials that were published more recently (normally referring to more recent medicines such as liraglutide and semaglutide)

have shown slightly higher levels in the tool. Although most of the trials were randomized and blind (96.8% double-blind), about half (n=50, 49.0%) of them did not adequately inform about the randomization process and allocation concealment. One-fourth of the studies (n=25; 24.5%) showed methodological concerns in relation to the selective bias, as they provided complete data for efficacy results only for participants who completed the study. On the other hand, most of the studies (n=87; 85.3%) analyzed the security results of intention-to-treat safety and considered the entire population. Most of the studies included (n=90; 88.2%) were sponsored by pharmaceutical companies or declared a conflict of interest with the research.

We were able to build two major network meta-analyses for the results of weight loss (absolute measurement) (n=55 studies) and incidence of serious adverse events (n=39 studies) (see Figure 2). All original networks were found to be robust in transitivity analysis (no node split analysis was possible due to the reduced number of studies per comparison in one node). For other outcomes, such as death and specific adverse events, no meta-analyses were performed, given the scarcity of data and the lack of standardized reporting of outcomes.

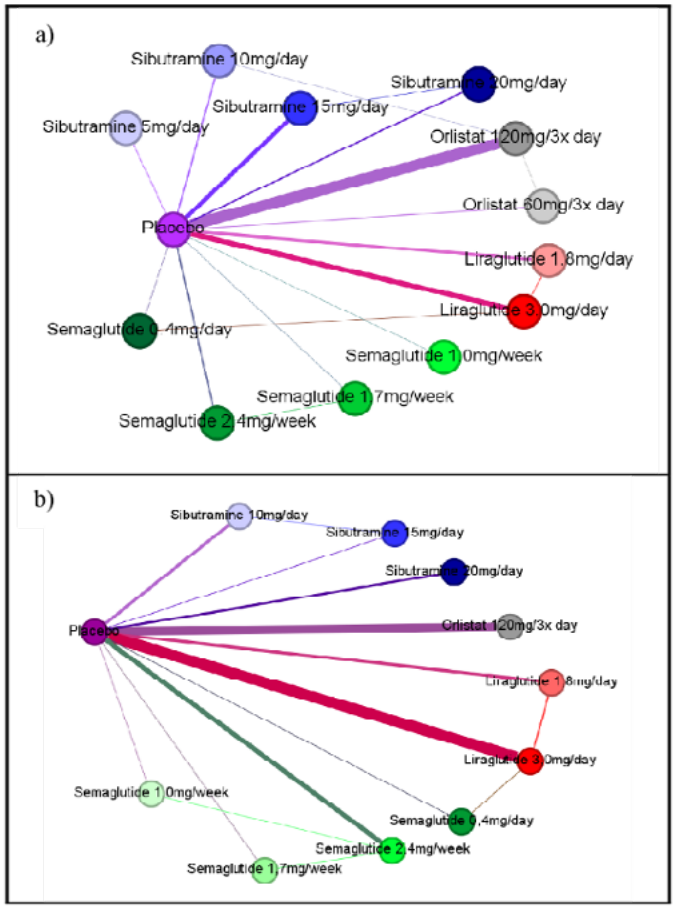

FIGURE 2 - Network graphics for key outcomes of interest (a) Efficacy measured as weight loss and (b) safety measured as the incidence of serious adverse events.

Footnote: Each circle (node) represents an intervention, and the lines represent direct comparisons. The colors represent drugs belonging to the same class.

All treatments were found to be significantly more effective than placebo in reducing patients' weight as demonstrated in Table I. The use of semaglutide (especially 0.4 mg/day and 2.4 mg/week) was statistically associated with a greater weight loss in comparison to all the other treatment interventions ($p<0.05$) (semaglutide 0.4 mg/day vs. placebo: SMD -14.33 Kg [95% CrI -17,3; - 11.5]). Sibutramine, when used in higher doses (10, 15, and 20 mg/day) also promoted a greater weight loss in comparison to liraglutide in smaller doses (1.8 mg/day) and to orlistat on both doses (60 and 120 mg/3x day). On the other hand, orlistat was considered superior to liraglutide 3.0 mg/day for this outcome. No significant differences were found between the interventions for the result of the incidence of serious adverse events (see Table I).

TABLE I - Comparison of multiple treatments of the effect of anti-obesity drugs on weight loss and the incidence of serious adverse events

Liraglutide 1.8 mg/day	-2,04 (-3,26, -0,84)	-0,05 (-1,27, 1,13)	0,03 (-1,88, 1,89)	2,82 (1,73, 3,89)	-11,55 (-14,61, -8,56)	-2,07 (-4,63, 0,34)	-2,79 (-5,70, 0,09)	-5,91 (-7,96, -4,01)	-2,46 (-4,36, -0,69)	-1,49 (-3,06, -0,05)	-2,43 (-4,33, -0,68)	0,10 (-2,46, 2,66)
0,89 (0,49, 1,72)	Liraglutide 3 mg/day	2,00 (1,02, 2,93)	2,04 (0,37, 3,82)	4,85 (4,04, 5,67)	-9,49 (-12,39, -6,65)	-0,04 (-2,46, 2,22)	-0,75 (-3,59, 1,99)	-3,86 (-5,77, -2,09)	-0,42 (-2,18, 1,26)	0,53 (-0,77, 1,82)	-0,40 (-2,11, 1,22)	2,14 (-0,32, 4,60)
0,73 (0,36, 1,41)	0,81 (0,49, 1,26)	Orlistat 120 mg/3x day	0,06 (-1,46, 1,67)	2,86 (2,36, 3,39)	-11,48 (-14,45, -8,58)	-2,03 (-4,37, 0,16)	-2,73 (-5,47, -0,08)	-5,86 (-7,64, -4,21)	-2,42 (-3,97, -0,95)	-1,45 (-2,61, -0,34)	-2,37 (-3,98, -0,86)	0,14 (-2,24, 2,53)
--	--	--	Orlistat 60 mg/3x day	2,79 (1,22, 4,29)	-11,55 (-14,82, -8,37)	-2,09 (-4,88, 0,53)	-2,82 (-5,93, 0,23)	-5,91 (-8,29, -3,77)	-2,48 (-4,73, -0,44)	-1,53 (-3,40, 0,25)	-2,45 (-4,67, -0,40)	0,08 (-2,74, 2,82)
0,96 (0,52, 1,70)	1,07 (0,75, 1,41)	1,32 (0,93, 1,85)	--	Placebo	-14,33 (-17,26, -11,51)	-4,89 (-7,15, -2,74)	-5,60 (-8,29, -2,97)	-8,72 (-10,44, -7,16)	-5,27 (-6,82, -3,84)	-4,33 (-5,35, -3,31)	-5,24 (-6,77, -3,81)	-2,71 (-5,03, -0,39)
0,86 (0,26, 3,15)	0,95 (0,32, 3,19)	1,19 (0,38, 4,17)	--	0,90 (0,32, 3,02)	Semaglutide 0.4 mg/day	9,44 (5,84, 13,05)	8,78 (4,75, 12,61)	5,63 (2,30, 8,86)	9,07 (5,85, 12,26)	9,99 (7,04, 13,05)	9,10 (5,90, 12,30)	11,64 (7,98, 15,31)
1,02 (0,40, 2,59)	1,14 (0,49, 2,47)	1,41 (0,62, 3,21)	--	1,06 (0,51, 2,27)	1,18 (0,29, 4,30)	Semaglutide 1 mg/week	-0,69 (-3,94, 2,52)	-3,82 (-6,09, -1,66)	-0,37 (-2,98, 2,26)	0,57 (-1,79, 3,02)	-0,34 (-3,00, 2,29)	2,16 (-0,95, 5,44)
0,38 (0,09, 1,32)	0,42 (0,12, 1,35)	0,52 (0,15, 1,68)	--	0,40 (0,12, 1,24)	0,44 (0,08, 2,03)	0,37 (0,10, 1,37)	Semaglutide 1.7 mg/week	-3,12 (-5,67, -0,55)	0,33 (-2,73, 3,30)	1,27 (-1,55, 4,14)	0,36 (-2,63, 3,36)	2,87 (-0,56, 6,40)
0,68 (0,33, 1,39)	0,76 (0,44, 1,23)	0,94 (0,55, 1,60)	--	0,71 (0,48, 1,06)	0,79 (0,22, 2,45)	0,67 (0,31, 1,38)	1,80 (0,58, 5,64)	Semaglutide 2.4 mg/week	3,45 (1,34, 5,63)	4,41 (2,55, 6,39)	3,46 (1,36, 5,72)	6,00 (3,25, 8,95)
0,81 (0,32, 1,74)	0,92 (0,40, 1,57)	1,12 (0,52, 2,06)	--	0,86 (0,42, 1,41)	0,93 (0,24, 3,10)	0,79 (0,28, 1,92)	2,08 (0,56, 7,91)	1,19 (0,53, 2,26)	Sibutramine 10 mg/day	0,96 (-0,79, 2,76)	0,02 (-2,00, 2,13)	2,56 (-0,11, 5,43)
0,65 (0,10, 5,87)	0,71 (0,11, 6,21)	0,89 (0,14, 7,71)	--	0,68 (0,11, 5,72)	0,75 (0,09, 8,18)	0,62 (0,08, 5,91)	1,72 (0,20, 19,21)	0,95 (0,14, 8,32)	0,82 (0,13, 7,18)	Sibutramine 15 mg/day	-0,93 (-2,62, 0,74)	1,60 (-0,87, 4,19)
0,58 (0,17, 1,86)	0,64 (0,20, 1,83)	0,80 (0,25, 2,34)	--	0,61 (0,20, 1,68)	0,68 (0,14, 2,87)	0,56 (0,16, 2,07)	1,54 (0,33, 7,51)	0,85 (0,28, 2,59)	0,73 (0,22, 2,47)	0,86 (0,08, 7,88)	Sibutramine 20 mg/day	2,53 (-0,19, 5,31)
--	--	--	--	--	--	--	--	--	--	--	--	Sibutramine 5 mg/day

Footnote: Multiple comparisons of treatments based on network-based consistency analysis of weight loss (upper quadrant - in green) and incidence of serious adverse events (back quadrant - in yellow). Treatments are represented in alphabetical order. Comparisons between treatments should be read from left to right, and the estimated proportion is in the common cell. For weight loss, the values are presented as standard mean difference (MDS) with a credible interval (Crl) of 95%; if SMD<0 favors the occurrence of the event for spine-defining treatment, whereas an SMD>1 favors line-defining treatment (e.g., liraglutide 1,8 mg/day vs. placebo has an SMD of 2,82 [95% Crl, 1,73 -3,89], demonstrating that the patients from the liraglutide group had lost more weight [statistically significant]). For serious adverse events, the values are in odds ratio (OR); if OR>, it favors the occurrence of the event for the spine-defining treatment, while an OR<1 favors the line-defining treatment (for example, Orlistat 120 mg/3x day vs. placebo shows an OR of 1,32 [95% Crl, 0,93-1,85] demonstrating that the patients in the liraglutide group may be more inclined to those events [not statistically significant]).

Probability ranks for the evaluated outcomes were performed. Figure 3 graphically correlates SUCRA results for weight loss (efficacy) and serious adverse events (safety). Overall, semaglutide at different doses had the highest probabilities of being the best treatment option considering the efficacy profile with SUCRA of around 70% for doses of 1.0 and 1.7 mg/week and 95% for doses of 0.4 mg/day or 2.4 mg/week. Sibutramine at higher doses (10, 15, and 20 mg/day) as well as higher doses of liraglutide 3 mg/day had an intermediate profile with probabilities of leading to weight loss of around 50-65%. On the other hand, lower doses of liraglutide, sibutramine, and any dose of orlistat were found to be less effective (probabilities around 20%). Placebo was the worst option (<1% probability). Regarding safety, although semaglutide 1.7 mg/week or 2.4 mg/week is more likely to cause serious adverse events, similar to orlistat and sibutramine at any dose (about 60-80% probability), semaglutide 0.4 mg/day or 1.0 mg/week and liraglutide were both less associated with these events (odds about 30-40%). Placebo was considered the safest option (25% SUCRA).

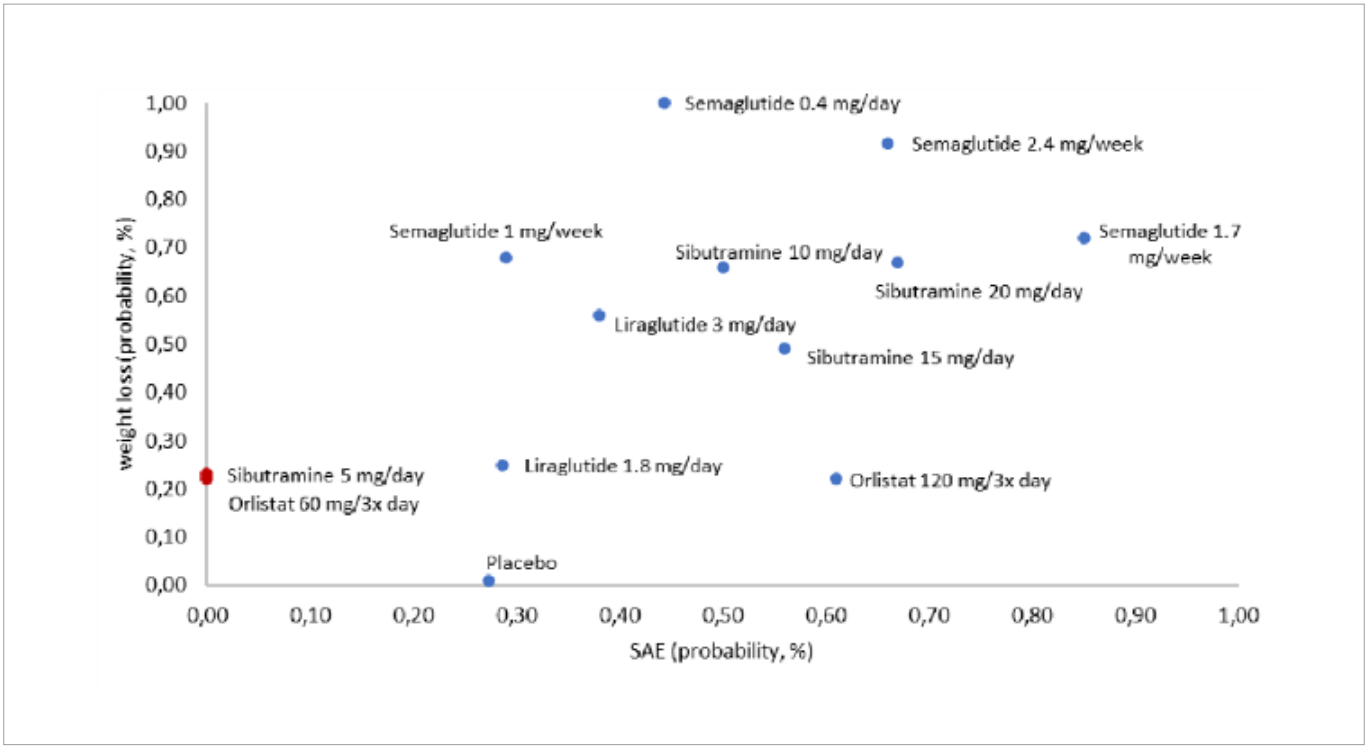

FIGURE 3 - Surface Analysis Under the Cumulative Curve (SUCRA) for the Outcomes of Interest - Efficacy (weight loss) and Safety (serious adverse events - SAE).

Footnote: Values are shown as percentages (%). No safety data are available for sibutramine 5 mg/day and orlistat 60 mg/3x day.

The results of SMAA were similar to those obtained by individual networks. The acceptability classification of scenario I (weight loss and incidence of serious adverse events with lack of preferences and orlistat 120 mg/3x day as baseline) is shown in Table 2A (comprising ten therapeutic options and placebo). This scenario favored semaglutide 0.4 mg/day (95% core weight benefit-risk ratio) followers by semaglutide 2.4 mg/week with an

overall risk-benefit ratio of 83%. Placebo and orlistat (120 mg/3x day) were disadvantaged options. When establishing ordinal preferences of the criteria (considering serious adverse events as the first important outcome followed by weight loss), the results remained similar, with semaglutide 0.4 mg/day taking first place (core weight risk-benefit ratio of 69%), followed by semaglutide 2.4 mg/week (60%) (data not shown). Placebo was the worst option again. Very similar results were obtained in scenario II (Table 2B) when using placebo as a baseline for the same risk-benefit criteria in both the missing preference and ordinal preference models (semaglutide 0.4 mg/day has shown the best risk-benefit relation [around 85-90%] followed by semaglutide 2.4 mg/week [around 70-80%] while orlistat 120 mg/3x and placebo had the worst performances, taking the last place.

TABLE II - Acceptability ranking of stochastic analysis of multicriteria acceptability

(A)

Alternativas	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Peso central
Liraglutide 1,8 mg/dia	1%	1%	2%	2%	4%	6%	11%	18%	29%	26%	0%	8%
Liraglutide 3 mg/dia	0%	1%	9%	21%	26%	24%	14%	4%	0%	0%	0%	2%
Orlistat 120 mg/3x dia	0%	0%	0%	0%	1%	2%	7%	16%	40%	33%	1%	0%
Placebo	0%	0%	0%	1%	1%	2%	2%	3%	6%	12%	72%	1%
Semaglutide 0,4 mg/dia	94%	2%	1%	0%	0%	0%	0%	0%	0%	1%	0%	94%
Semaglutide 1 mg/semana	2%	5%	23%	18%	15%	13%	12%	9%	2%	1%	0%	11%
Semaglutide 1,7 mg/semana	0%	1%	19%	11%	8%	8%	11%	10%	7%	11%	13%	1%
Semaglutide 2,4 mg/semana	1%	83%	6%	3%	2%	1%	1%	1%	1%	0%	0%	4%
Sibutramine 10 mg/dia	0%	2%	21%	21%	19%	15%	12%	6%	2%	1%	0%	3%
Sibutramine 15 mg/dia	2%	3%	5%	6%	8%	12%	18%	22%	6%	8%	9%	12%
Sibutramine 20 mg/dia	0%	1%	14%	16%	15%	16%	13%	9%	6%	6%	4%	3%

Final rank	1	2	3	4	5	6	7	8	9	10	11
	Semaglutide 0,4 mg/dia	Semaglutide 2,4 mg/semana	Semaglutide 1 mg/semana	Liraglutide 3 mg/dia	Sibutramine 10 mg/dia	Sibutramine 20 mg/dia	Semaglutide 1,7 mg/semana	Sibutramine 15 mg/dia	Liraglutide 1.8 mg/dia	Orlistat 120 mg/3x dia	Placebo

(B)

Alternativas	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Peso central
Liraglutide 1,8 mg/dia	0%	2%	2%	3%	4%	6%	11%	18%	30%	24%	0%	10%
Liraglutide 3 mg/dia	0%	2%	9%	21%	27%	23%	13%	4%	0%	0%	0%	2%
Orlistat 120 mg/3x dia	0%	0%	0%	0%	1%	3%	7%	16%	39%	33%	1%	0%
Placebo	0%	0%	1%	1%	2%	2%	3%	3%	6%	12%	71%	2%
Semaglutide 0,4 mg/dia	94%	2%	1%	1%	0%	0%	0%	1%	1%	1%	0%	95%
Semaglutide 1 mg/semana	2%	4%	24%	17%	13%	13%	12%	9%	3%	2%	0%	14%
Semaglutide 1,7 mg/semana	0%	1%	19%	11%	8%	9%	10%	11%	6%	11%	14%	1%
Semaglutide 2,4 mg/semana	1%	83%	5%	3%	2%	2%	2%	1%	1%	0%	0%	5%
Sibutramine 10 mg/dia	0%	2%	20%	22%	19%	16%	11%	6%	2%	1%	0%	3%
Sibutramine 15 mg/dia	2%	3%	5%	6%	9%	12%	18%	21%	7%	9%	9%	16%
Sibutramine 20 mg/dia	0%	1%	14%	17%	15%	15%	13%	9%	6%	6%	4%	4%

Final rank	1	2	3	4	5	6	7	8	9	10	11
	Semaglutide 0,4 mg/dia	Semaglutide 2,4 mg/semana	Semaglutide 1 mg/semana	Liraglutide 3 mg/dia	Sibutramine 10 mg/dia	Sibutramine 20 mg/dia	Semaglutide 1,7 mg/semana	Sibutramine 15 mg/dia	Liraglutide 1.8 mg/dia	Orlistat 120 mg/3x dia	Placebo

Footnote: Each intervention has a chance of being the best (rank 1) or the worst treatment (rank 11) globally considering its benefits and risks (weight loss and serious adverse events; missing preference models). Scenario 1: Orlistat 120 mg/3x day as baseline; Scenario 2: Placebo as a baseline.

The certainty of the evidence (GRADE approach) for the comparisons of the different therapeutic regimens vs. placebo varied from moderate to high for the two outcomes of interest; pitfalls were mostly related to the low methodological quality of some trials (e.g., risk of bias) and small number of available studies for some comparisons (i.e., poor direct evidence, potential data inconsistency) (see supplementary material).

DISCUSSION

This network meta-analysis involving 102 ECRs with 45.047 participants allowed the creation of a probability ranking in which semaglutide in any dose has proved itself to be the most efficient agent for weight reduction in obese and overweight patients. Next, the most prominent drugs were sibutramine in bigger doses (10, 15, and 20 mg/day) and liraglutide 3 mg/day with intermediate chances of promoting weight reduction. It was also possible to observe the most disadvantageous options, which were orlistat at any dose, sibutramine 5 mg/day and liraglutide 1.8 mg/day.

We found that the incidence of serious adverse events was overall similar across treatments – being mostly related to drugs' mechanism of action, without meaningful differences between active drugs and placebo. Few fatal events have been reported with these treatments. In fact, GLP-1 analogs such as liraglutide and semaglutide are often associated with biliary (cholelithiasis, cholecystitis) and hepatic disorders, and pancreatitis, which should be carefully addressed by clinicians according to the patients' clinical profile and preferences (Garvey *et al.*, 2022; Davies *et al.*, 2021). Orlistat is usually associated with serious gastrointestinal tract symptoms (e.g., diarrhea, cholelithiasis, and diverticulitis), while sibutramine can lead to blood pressure alterations and non-fatal cardiovascular events (e.g., stroke, acute myocardial infarction) (Torgerson *et al.*, 2004; Rössner *et al.*, 2000; James *et al.*, 2010), suggesting physical and biochemical parameters to be routinely monitored in these patients for early detection of possible serious adverse effects during treatment.

The created evidence is consistent with data from previous meta-analyses, where the analogs of GLP-1 demonstrated to be superior to other medications. A meta-analysis published in 2023 concluded that semaglutide 2.4 mg/week was better than all the interventions evaluated and allowed a weight loss of 5% of the previous weight of all the patients who had used the medicine (Iannone *et al.*, 2023). In another meta-analysis with 59.938 participants, semaglutide showed high efficacy and a similar safety profile to other anti-obesity medications (Smith *et al.*, 2022).

The worst treatment option was orlistat, corroborating the findings of previous reviews (Shi *et al.*, 2022; Khera *et al.*, 2016). This option was definitely not superior to usual care, (lifestyle modifications), not being able to reach the clinically relevant threshold (MID) of baseline weight loss of 5% (Brazilian Society of Hypertension, Brazilian Society of Cardiology, Brazilian Society of Endocrinology and Metabolism, Brazilian Diabetes Society, Brazilian Society of Obesity Studies, 2005; Brazilian Diabetes Society, 2019).

Sibutramine (10 and 20 mg/day) was better than liraglutide (1.8 and 3.0 mg/day) in terms of efficiency results with smaller costs considering the CMED list (Ministry of Health, 2023). However, the medicine has not been approved by the FDA since 2010, after the publication of a study that demonstrated that sibutramine is inappropriate for the hypertense population and that it could elevate the risk of non-fatal adverse events, such as acute myocardial infarction and strokes (Food and Drug Administration, 2010; James *et al.*, 2010). On the other hand, in Brazil, the medicine is allowed as long as it is prescribed in an appropriate prescription formulary, being up to the doctor the evaluation of the risk-benefit for each patient individually (National Health Surveillance Agency, 2014).

The 20 mg/day sibutramine dose is not recommended due to its higher risk of causing the development of adverse events (James *et al.*, 2010), but in our analyses,

it was possible to verify that the 10 mg/day dose was able to cause the same weight loss percentage with a lower incidence of adverse events (Figure 3), corroborating the prescription of smaller doses.

A meta-analysis with 49.810 participants assessed all the therapeutic options used for obesity (approved and discontinued) and obtained consistent results with what we have found, being semaglutide 2.4 mg/week and sibutramine associated with changes in lifestyle the best options for obesity and overweight management (Morsali *et al.*, 2023).

The sensibility analysis has shown that the network meta-analysis (direct and indirect) results were consistent, which provides additional support for the final evidence. A robust result guarantees the precision and trustworthiness of the results obtained, subsidizing its use in the updating of the therapeutic guidelines and protocols that can assist in the clinical decision-making of health professionals.

Guidelines from the United States of America and the United Kingdom highlight semaglutide in their recommendations, given the magnitude of the profit promoted by the medication and recall that its adverse events are related to the mechanism of action and that this fact can be mitigated by dose titration at the beginning of the treatment (Grunvald *et al.*, 2022; Shi *et al.*, 2022; National Institute for Health and Care Excellence, 2023).

The recommendations from Canada and Europe do not mention semaglutide, only liraglutide, naltrexone-bupropion, and orlistat as options for weight control for adults (Wharton *et al.*, 2020; Durrer *et al.*, 2019). The use of orlistat is strongly discouraged in the USA Guidelines due to its modest weight loss and the high incidence of adverse events (Shi *et al.*, 2022).

It is unanimous among the guidelines that pharmacotherapy should only be initiated when the individual cannot reach the weight loss goals by making use of lifestyle changes when the person reaches a *plateau* in the weight loss process, or when they show comorbidities associated with obesity (Brazilian Association for the Study of Obesity, 2016; Grunvald *et al.*, 2022; NHLBI Obesity Education, 2023; National Institute for Health and Care Excellence, 2023; Wharton *et al.*, 2020; Durrer *et al.*, 2019).

Regarding weight control for children, the United Kingdom recommends the use of orlistat only for children older than 12 years old, being allowed to be used by kids younger than 12 years old only in extreme cases and with associated comorbidities (National Institute for Health and Care Excellence, 2023). New guidelines published by the American Pediatric Academy mentioned the use of orlistat, phentermine-topiramate, and liraglutide for children older than 12 years old. Other medicines such as metformin and setmelanotide were mentioned but are not approved for weight control. Even so, the guideline reiterates that the medications should not be used as monotherapy and that those responsible for prescribing the drug should refer the individuals to intensive behavioral interventions (Hampl *et al.*, 2023).

Lastly, our study brings the stochastic analysis of multicriteria acceptability as a bigger contribution, which allows a clearer understanding of the best and worst options of prescription to manage obesity, considering the risk-benefit of each intervention evaluated, besides providing robust evidence for the update of the guidelines that still haven't added semaglutide in their therapeutic arsenal and to reevaluate sibutramine as a therapeutic option for patients without hypertension. New studies including different drugs that were not addressed in this research, such as naltrexone-bupropion, phentermine/topiramate, and tirzepatide, might be relevant. The limitations of our review include the lack of details on the scientific reports of the older studies (orlistat and sibutramine), and there might be biases that were not identified due to lack of information. The studies also varied in population characteristics and follow-up time, but sensitivity analyses confirmed the robustness of the evidence generated. Both the limitations described were also mentioned in previous meta-analyses (Arterburn *et al.*, 2004; Khera *et al.*, 2016). Our network meta-analysis was created before the publication of any results from the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA about the risk of suicidal thoughts and thoughts about self-harm with agonists from the receptors

GLP-1 (European Medicines Agency, 2023). These results might have an impact on this study's conclusions.

ACKNOWLEDGMENTS

We would like to thank the Post Graduate Program in Pharmaceutical Sciences from UNIOESTE for supporting our research.

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Received for publication on February 29th, 2024
Accepted for publication on May 05th, 2024
Associated Editor: Silvya Stuchi Maria-Engler