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Tirzepatide vs Semaglutide for Weight Loss in Obese Patients: A Systematic Review of Effectiveness, Safety, and Tolerability

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Abstract:
Obesity and overweight represent pressing global health concerns, with their mitigation posing a formidable challenge. Among the numerous strategies employed to tackle these conditions, the effectiveness of pharmacological interventions like Semaglutide and Tirzepatide has garnered significant attention. This research aims to provide a thorough examination of the efficacy, safety, and tolerability of Tirzepatide and Semaglutide in promoting weight loss among obese patients. This study meticulously reviewed all relevant experiments involving anti-obesity medications across multiple reputable databases. Sensitivity analyses were conducted using various robust techniques such as the Bucher method, applying different estimands and time points to ensure the accuracy and reliability of the findings. The results revealed that subcutaneous administration of Tirzepatide and Semaglutide led to significant reductions in BMI, body weight, and waist circumference compared to control groups. Notably, the 15 mg dose of Tirzepatide achieved the most substantial weight loss. While Tirzepatide and Semaglutide are not yet directly comparable in their entirety for weight management, this study utilized a matching-adjusted indirect treatment comparison approach to evaluate their effectiveness. The findings indicate that Tirzepatide demonstrates superior efficacy in weight reduction compared to Semaglutide, highlighting its potential as a more effective pharmacological option for managing chronic obesity.
Keywords: GLP-1, Obesity, Semaglutide, Tirzepatide, Weight loss

Introduction: Overweight and obesity have almost tripled in prevalence during the 1970s, greatly increasing the cost of healthcare worldwide. Obesity is linked to higher risks of type 2 diabetes, certain malignancies, cardiovascular disease (CVD), shortened life expectancy, and a lower standard of living [1].

According to various researches, blood pressure, lipid profiles, and blood glucose may all improve with at least 5% of body weight loss. Significant weight reduction, especially over 10%, may lower the risk of comorbidities associated with obesity. Clinical recommendations suggest that the first line of therapy for obesity should be lifestyle improvements, such as increased physical activity, decreased calorie consumption, and behavioural changes. Long-term lifestyle modifications may result in 3-5% weight reduction; however, it is sometimes difficult to achieve and sustain more significant weight loss [2,3].

In cases when lifestyle modifications alone have not resulted in sustained weight reduction, medication may be an option for adults with a body mass index of 30 kg/m^2 or above, or 27 kg/m^2 with at least one obesity-related medical condition. One of the first drugs licensed for weight loss was liraglutide, a daily subcutaneous GLP-1 receptor agonist that demonstrated an average weight loss of 5–6 kg [4]. Tirzepatide and Semaglutide have surfaced as potential therapies more recently.

Semaglutide, a once-weekly given GLP-1 RA with a longer half-life than liraglutide, has shown superior efficacy in aiding weight reduction and regulating blood sugar levels. In addition to being approved for the treatment of type 2 diabetes, it was also given approval in 2021 and 2022 for the management of obesity in people who had at least one weight-related comorbidity. Semaglutide 2.4 mg has been demonstrated in studies to dramatically lower cardiovascular events in obese individuals without diabetes. [5].

Glycaemic control and body weight reduction in individuals with type 2 diabetes have been shown to be enhanced by tirzepatide, a dual agonist of GLP-1 and GIP receptors. It was first authorized in 2022 to treat diabetes, then in November 2023, it was given further clearance to treat obesity at doses of up to 15 mg per week [6,7].

The effectiveness of Semaglutide may have been underestimated in the past when it came to obese or overweight people without diabetes since lower doses and shorter treatment periods were employed than those that are presently authorized [8]. Furthermore, individuals with type 2 diabetes have been the primary target of Tirzepatide systematic reviews. Furthermore, while BMI is a helpful indicator of obesity at the population level, it ignores factors like body composition and fat distribution that are vital for determining the metabolic hazards linked to obesity [9].

Therefore, in order to determine the efficacy and safety of subcutaneous Tirzepatide and Semaglutide at dosages that have been authorized for the treatment of obesity, we carried out a thorough review and statistical analysis. In overweight and obese people who have received treatment for at least a year, our study focuses on weight loss, decrease in waist circumference, and other health outcomes.

Methodology:

Search-strategy: This study followed to the "Preferred Reporting Items for Systematic Review and Meta-analysis" guidelines. All-inclusive search was conducted in the PMC, PubMed, MDPI, Cochrane library and Science directcovering the period from January 2020 to April 2024. The examples of search strategies used in the PubMed search database and other databases are

demonstrated in Table 1. To identify any possibly neglected eligible trials, we additionally manually scrutinized the lists of the identified journals and related review studies.

Table 1: Search Strategy for various databases

Search Stratergy	**Database Used**	**Numbers of papers identified**
Semaglutide AND Tirzepatide	PubMed Simple search	40
("Obesity/drug therapy"[Majr] OR "Obesity/prevention and control"[Majr] OR "Obesity/therapy"[Majr]) AND semaglutide AND tirzepatide	PubMed MeSH Stratergy	04
((Semaglutide[Title/Abstract]) AND (Tirzepatide[Title/Abstract])) AND (Obesity[Text Word])	PubMed Advanced Search	27
Tirzepatide in Title Abstract Keyword AND Semaglutide in Title Abstract Keyword AND Obesity in All Text	Cochrane Library advanced search	21
((semaglutide[Abstract]) AND tirzepatide[Abstract]) AND obesity[Text Word]	PMC Advanced Search	52
Semaglutide AND Tirzepatide AND Obesity	Science Direct Advanced Search	121
Semaglutide AND Tirzepatide	MDPI search	05
		270

Eligibility criteria: The eligibility criteria for this analysis included papers written and published in English that focus on comparisons between Semaglutide and Tirzepatide in obese individuals. The papers needed to be open access, available in full text, and peer-reviewed. Excluded from the analysis were grey literature, papers focusing on ICU patients and pregnant women, letters to the editor, and studies conducted on animals.

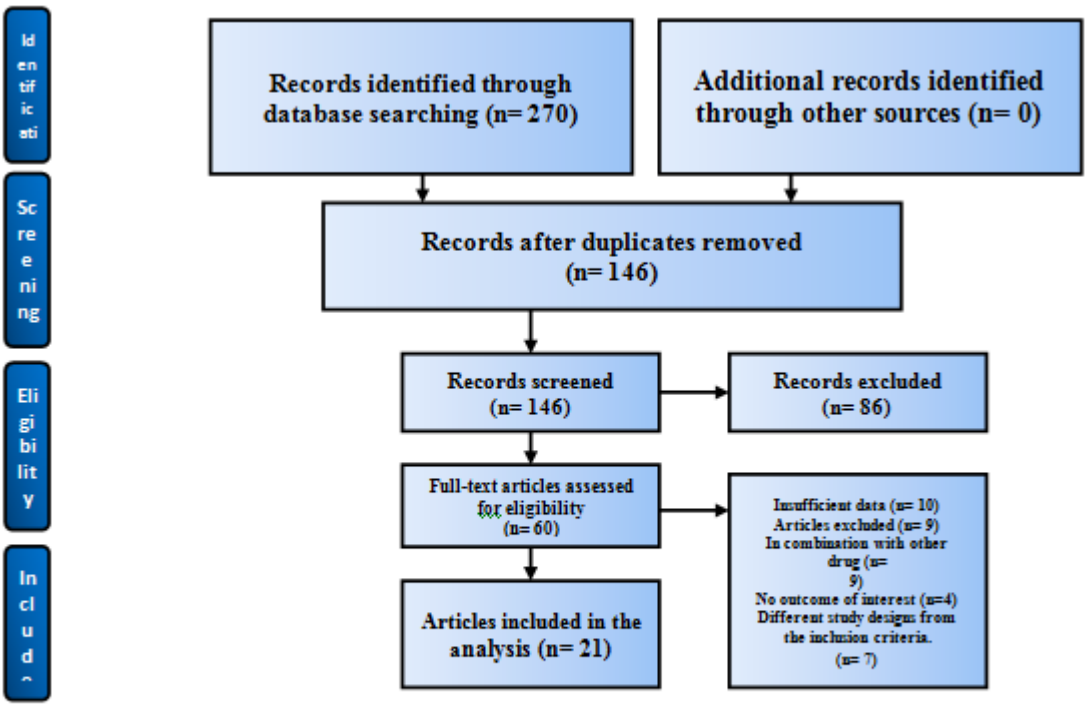

Figure 1: Flow chart of the research selection procedure using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Data extraction: Two writers conducted a separate and unbiased evaluation of the qualifying studies. The study's site, the year of publication, the first author's title, and the study design were all extracted. Of particular interest were the means and standard deviations of the intended outcomes at the start of the study, following the intervention, and/or comparing the two time points. participant characteristics, the kind of outcomes examined, the period of the intervention, the dose of the intervention, and other factors; the size of the sample for both the intervention and control groups.

Quality assessment of selected articles: Figure 2 shows the comprehensive assessment of bias in the comprised studies using the RoB2 method. The assessment of bias was conducted across five domains, categorized as low (green), moderate (yellow), or high (red) risk of bias. All the studies included in the analysis were determined to have a minimal risk of bias in each of the five areas. This is because they had a well-designed randomization process, minimal deviations from the intended intervention, a low amount of missing outcome data, high-quality measurement of the outcome, and a low risk of bias in selecting and reporting the results. Consequently, all of them were considered to have a generally low risk of bias.

Figure 2. Evaluation of the listed studies' bias risk

Statistical analysis and data synthesis: The statistical analyses were conducted for specifically Review Manager version 5.4.1.54. Efficiency studies were conducted using the intention-to-treat population for all outcomes. The treatment policy estimate, obtained by classic intention-to-treat analysis, was derived from the trials. This estimate measures the treatment response for all individuals who were randomly assigned, regardless of whether they discontinued treatment or received further interventions. The combined effects of Semaglutide and Tirzepatide, both alone and in combination, on the percentage change in body weight and the change in waist circumference in centimetres were calculated using either fixed-effect, depending on the level of heterogeneity. The variability among the experiments was evaluated using the I 2 statistic. An I 2 value more than 50% was considered indicative of significant heterogeneity. The chosen threshold of significance was established at <0.05.

Results

Study selection: Figure 1 shows a flowchart outlining the approach for selecting studies, including the criteria used for excluding certain ones. According to this figure, the electronic databases indicated before generated a total of 270 articles. After eliminating duplicate studies, the total number of papers was 146. After examining the titles and abstracts of the study, 86 articles were excluded since they did not meet the inclusion criteria. During the secondary screening, a total of 60 articles were identified using the full-text. 39 studies were excluded for

the reasons outlined before. Ultimately, a total of 21 publications, each including 45 treatment arms, were included in the quantitative analysis after meeting the necessary criteria.

Study characteristics: Table 1. displays the characteristics of the combined articles. Our surveys indicate that researches were carried out in a multi-country or multi-centre fashion. All studies were published within the timeframe of 2020 to 2024. All studies employed a similar design, and the follow-up interference lasted between 12 and 15 months. At the baseline, the age of participants varied from 45 to 70 years. The duration of studies varied between 1 to 4 months. Additionally, the intervention dosages varied between 1 and 15 mg when administered subcutaneously.

Table 1. Characteristics of the studies that were included

Sr. no.	Authors' name	Study name	Years	Sample size	Study duration	Results	Ref.
1.	Ding et al.,	"Evaluation and comparison of efficacy and safety of Tirzepatide and Semaglutide in patients with type 2 diabetes mellitus: A Bayesian network meta-analysis"	(2023)	_	3-4 months	Both Tirzepatide and Semaglutide exhibited excellent antidiabetic benefits in overweight or obese entities with T2D.	[10]
2.	Lampasas et al.,	"The catcher in the gut: Tirzepatide, a dual incretin analog for the treatment of type 2 diabetes mellitus and obesity"	(2022)	_	3-4 months	Tirzepatide, a dual incretin analog, improves glycemic management and weight loss through GLP-1 and GIP receptors	[11]
3.	Azuri et al.,	"Tirzepatide versus Semaglutide for weight loss in patients with type 2 diabetes mellitus: A value for money analysis"	(2023)	_	4 months	Weight loss with Tirzepatide is cheaper than with Semaglutide.	[12]
4.	Colin et al.,	"Once-weekly 2.4 mg Semaglutide for Weight Management in Obesity: A Game Changer?"	(2022)	_	3-4 months	Regulatory bodies authorized Semaglutide for obesity management; however, modern drugs may provide greater long-term weight reduction	[13]

5.	Heise et al.,	"Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes"	(2023)	_	4 months	Tirzepatide effectively energy intake, reduces appetite, and fat mass, contributing to weight loss	[14]
6.	Jung et al.,	"The Upcoming Weekly Tides (Semaglutide vs. Tirzepatide) against Obesity: STEP or SURPASS?"	(2022)	_	2 months	Review of safety, glycemic control, and effectiveness of Tirzepatide and Semaglutide in body weight reduction.	[15]
7.	Lazzaroni et al.,	"Anti-diabetic drugs and weight loss in patients with type 2 diabetes"	(2021)	_	3-4 months	Demonstrates that type 2 diabetics have the highest weight reduction while using new anti-diabetic medications like Tirzepatide and GLP1-RA.	[16]
8.	le Roux et al.,	"Tirzepatide 10 and 15 mg compared with Semaglutide 2.4 mg for the treatment of obesity: An indirect treatment Comparison"	(2023)	_	1 months	Tirzepatide 10 and 15 mg produced a higher reduction in weight than Semaglutide 2.4 mg	[17]
9.	Lingvay et al.,	"Achievement of glycemic targets with weight loss and without hypoglycemia in type 2 diabetes with the once-weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist Tirzepatide: A post	(2022)	_	2 months	Tirzepatide-treated T2D patients achieved clinically significant glycemic and weight loss goals more often than comparison groups in the SURPASS trials.	[18]

		hoc analysis of the SURPASS-1 to -5 studies."					
10.	Mody et al.,	"Cost per Patient Achieving Treatment Targets and Number Needed to Treat with Tirzepatide Versus Semaglutide 1 mg in Patients with Type 2 Diabetes in the United States"	(2023)	_	3-4 months	Tirzepatide may assist patients with type 2 diabetes in meeting glycemic, weight loss, and composite therapy objectives at a lower cost per responder compared to Semaglutide	[19]
11.	Müllertz et al.,	"Potent incretin-based therapy for obesity: A systematic review and meta-analysis of the efficacy of Semaglutide and Tirzepatide on body weight and waist circumference, and safety"	(2024)	_	2 months	Semaglutide combined with Tirzepatide leads to excellent tolerability and significant weight and waist circumference reductions	[20]
12.	Nauck et al.,	"Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycemic control and body weight reduction"	(2023)	_	5 months	Tirzepatide appears to outperform GLP-1 RAs, reviving interest in GIP for treating type 2 diabetes and obesity	[21]
13.	Ryan et al.,	"Next Generation Ant obesity Medications: Semaglutide, Semaglutide, Tirzepatide and Bimagrumab: What do They Mean for Clinical Practice?"	(2021)	_	1 months	Discusses the implications of new anti-obesity medications, including Tirzepatide and Semaglutide, for clinical practice	[22]

14.	Sinha et al.,	"Efficacy and Safety of Tirzepatide in Type 2 Diabetes and Obesity Management"	(2023)	_	2 months	The SURMOUNT-1 trial reveals that Tirzepatide is revolutionizing T2DM and obesity management	[23]
15.	Stretton et al.,	"Weight loss with subcutaneous Semaglutide versus other glucagon-like peptide 1 receptor agonists in type 2 diabetes: a systematic review"	(2023)	_	3-4 months	Semaglutide is more effective than other GLP-1 RAs for weight loss in T2D, but Tirzepatide is more effective overall.	[24]
16.	Vadher et al.,	"Efficacy of Tirzepatide 5, 10 and 15 mg versus Semaglutide 2 mg in patients with type 2 diabetes: An adjusted indirect treatment comparison"	(2022)	_	3-4 months	Tirzepatide 10 and 15 mg showed better HbA1c and weight reductions than Semaglutide 2 mg; Tirzepatide 5 mg showed similar results.	[25]
17.	Popoviciu et al.,	"Emerging Role of GLP-1 Agonists in Obesity: A Comprehensive Review of Randomized Controlled Trials."	(2023)	_	2 months	Based on long-term follow-up research, we discuss these drugs' pleiotropic effects, indications, contraindications, and precautions for diabetics and non-diabetics.	[26]
18.	Wadden et al.,	"The Role of Lifestyle Modification with Second-Generation Anti-obesity Medications: Comparisons, Questions, and Clinical Opportunities"	(2023)	_	3 months	Lifestyle modification may shift from calorie restriction to helping patients adopt dietary and activity patterns that support ideal body composition and health with the new AOMs.	[27]
19.	Urva et al.,	"The novel dual glucose-dependent insulinotropic	(2020)	_	3 months	The data indicate that Tirzepatide's effect on GE is	[28]

		polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist Tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists"				similar to GLP-1RAs selective.	
20.	Várkonyi et al.,	"Perspectives on weight control in diabetes – Tirzepatide"	(2023)	_	4 months	These data imply that Tirzepatide's clinical profile for T2D diabetes treatment is influenced by significant weight reduction and concomitant alterations.	[29]
21.	Melson et al.,	"Future therapies for obesity"	(2023)	_	3-4 months	We explore developing gut hormone combination obesity treatments and multimodal obesity therapy in this study.	[30]

Analysis results: The combined outcomes of the random-effects model demonstrated that, in comparison to the control group, subcutaneous Tirzepatide significantly decreased body weight (weighted mean difference): -11.24 kg, 95% confidence interval (CI): -11.29 to -9.38, P<0.001), waist circumference (WC), and BMI (WMD: -2.13 kg/m2, 95% CI: -4.26 to -1.82, P<0.001). Subgroup analysis showed that compared to lesser dosages of 10 mg and 5 mg (WMD: -9.08 kg, I2 = 92.2%, 95% CI: -10.75 to -7.42), weight loss was more substantial at a dose of 15 mg of subcutaneous Tirzepatide (WMD: -12.02 kg,95% CI: -14.35 to -10.68, I2 = 96.1%,). Furthermore, there was a significant difference in weight, BMI, and WC across the trials.

Evaluation of sensitivity: In order to assess the influence of every article on the overall effect size for BMI, weight, and WC levels, we meticulously removed every experiment from the examination. The robustness and consistency of the results were shown by the leave-one-out sensitivity analysis.

Efficacy: Comparing a placebo to a lowered HbA1c, Tirzepatide 15 mg was the most effective treatment (MD [95% CI]: −21.61 mmol/mol [−22.26 to −18.97]). After then, Semaglutide 0.5 mg (−11.00 mmol/mol), Semaglutide 10 mg (−21.19 mmol/mol), Tirzepatide 5 mg (−17.60

mmol/mol), and Semaglutide 2.0 mg (−16.74 mmol/mol) were contributed. When HbA1c was measured in mmol/mol, all Tirzepatide doses outperformed Semaglutide 1.0 mg and 0.5 mg and were comparable to Semaglutide 2.0 mg. ESM shows the effect sizes (MD [95% CI]) for Tirzepatide 15 mg vs. Semaglutide 2.0 mg, Tirzepatide 10 mg vs. Semaglutide 1.0 mg, and Tirzepatide 5 mg vs. Semaglutide 0.5 mg; These were -4.94 (-6.55 to -3.23); -5.12(-7.21 to -3.48); and -5.60 (-7.50 to -3.60) mmol/mol respectively. When HbA1c was expressed as a percentage, ESM found that Tirzepatide at dosages of 15 mg, 10 mg, and 5 mg was more successful than Semaglutide at doses of 1.0 mg (MD = −0.45%), 2.0 mg (MD = −0.38%), and 0.5 mg (MD = −0.51%). The confidence in estimates for comparisons between Tirzepatide and Semaglutide varied from high to moderate, with the exception of comparisons involving Semaglutide 2.0 mg, where the estimates' confidence was often low. The results of the analysis indicated that the drug with the best likelihood of lowering HbA1c was Tirzepatide 15 mg.

The two types of medications that helped patients reach the HbA1c target of ≤48 mmol/mol (≤6.5%) in comparison to placebo were Tirzepatide 15 mg (risk ratio = 7.02) and Semaglutide 2.0 mg (risk ratio = 7.63). In contrast, Tirzepatide 5 mg outperformed Semaglutide 0.5 mg, while Tirzepatide 15 mg and 10 mg beat Semaglutide 1.0 mg and 0.5 mg in inter-drug comparisons.Comparing the efficacy of the most effective medicines against a placebo with a HbA1c goal of less than 53 mmol/mol (less than 5%) was possible with Tirzepatide (15 mg; risk ratio = 3.71) and Semaglutide 2.0 mg (20 mg). All Tirzepatide doses were better than Semaglutide 0.5 mg, however there were no differences seen between any of the Tirzepatide dosages and Semaglutide 2.0 mg or 1.0 mg.

Serious adverse events and severe hypoglycaemia: When compared to a placebo, neither Tirzepatide nor Semaglutide showed an increased risk of significant side effects. Furthermore, no significant differences were seen when Tirzepatide and Semaglutide were compared. Since there were no events in the majority of treatment arms across all trials, a meta-analysis for severe hypoglycaemia was not conducted. In the population as a whole, 107 people had a severe hypoglycaemia event; thirty of these incidents occurred in a single trial arm when participants were given postprandial insulin.

Discussion: Tirzepatide and Semaglutide 2.4 mg are new classes of extremely effective ant obesity medications that cause weight decreases of 15% or more.[31] This is the first study comparing the effects of tirzepatide 10 and 15 mg with Semaglutide 2.4 mg on the percentage change in body weight and participants achieving 5% or more drop in body weight from baseline in obese, overweight, and non-diabetic persons. Studies comparing Tirzepatide 10 and 15 mg to Semaglutide 2.4 mg showed additional weight reduction of 4.0%–5.6% and 5.4%–6.8%, respectively. This consistent with the finding that while taking tirzepatide at dosages of 10 or 15 mg, as compared to Semaglutide at 2.4 mg, people were more likely to lose 5% or more of their body weight. In the absence of a head-to-head research, data on comparative efficacy may help doctors make relevant therapeutic decisions to support tailored therapy and inform pharmacoeconomic assessments once tirzepatide is approved for chronic weight management[32].

Clinical outcomes for obese individuals have been shown to improve with intentional weight reduction, and larger weight losses are associated with further advantages. For instance, long-term weight reduction of 5% to 16% may lead to improvements in metabolic health and weight-related problems, including cardiovascular risk factors, quality of life, depression, genitourinary function, and fertility, among other things, that are clinically important.[33] Future research will be necessary, but it is reasonable to assume that the disparity in weight loss rates

seen in the clinical trials for tirzepatide 15 mg (20.9%) and Semaglutide 2.4 mg (16.9%) could lead to different clinical benefits, given the correlation between weight loss magnitude and clinical outcomes benefit. In this ITC, the difference in body weight decrease between tirzepatide 10 and 15 mg and Semaglutide 2.4 mg was 4.7% and 5.9%, respectively. RCTs with sufficient power to evaluate the effects of weight reduction on mortality and long-term outcomes will provide the most reliable information.

There is uncertainty about the mechanism(s) by which tirzepatide reduces body weight more than Semaglutide 2.4 mg. Tirzepatide likewise activates GIP receptors and possesses the same GLP-1 RA17 characteristic as semaglutide. GLP-1 controls body weight both peripherally and centrally[34]. Similar to this, it is believed that GIP receptors control hunger and food intake via modifying their distribution and central nervous system signaling, which in turn controls body weight.[35] Additionally, Tirzepatide has been shown to postpone stomach emptying; however, this effect is not believed to be the primary cause of weight loss and diminishes with prolonged use.[36] Results on stomach emptying for Semaglutide have been inconsistent.[37] While the precise characteristics of the drugs that contribute to the observed variations in efficacy remain unclear, the various modes of action provide a plausible factor that warrants examination in further investigations.

Research conducted on T2D patients supports the findings seen here. In a randomized clinical study with open-label treatment for type 2 diabetes, tirzepatide at all dosages (5, 10, and 15 mg) reduced body weight and HbA1c more than Semaglutide at 1 mg. Similarly, tirzepatide 10 and 15 mg led to significantly larger reductions in body weight and HbA1c than Semaglutide 2.0 mg, but there were no significant differences between tirzepatide 5 mg and Semaglutide 2.0 mg, according to an ITC leveraging data from the SURPASS-2 and SUSTAIN FORTE trials.[38] The data generally support the idea that tirzepatide causes greater decreases in body weight than semaglutide, even though the studies compared and described here were not intended to be weight loss trials and the Semaglutide dosages varied.

Adverse events were not analyzed since it is inherently difficult to utilize ITCs to compare safety and tolerability data due to variations in the safety data gathering process. For instance, open-ended questions, check-box surveys, or oral interrogations by the investigator team may all be used to gather safety data. Furthermore, STEP 1 was finished in early 2021, however the bulk of the SURMOUNT-1 experiment was carried out between 2019 and 2022, during the COVID-19 pandemic. According to the primary research articles, comparable proportions of individuals reported experiencing any side effects with Tirzepatide 10 mg (81.8%), Tirzepatide 15 mg (78.9%), and Semaglutide 2.4 mg (89.7%). The most frequent side effects were gastrointestinal (constipation, diarrhea, and nausea). The gastrointestinal events were mild to moderate in severity, transient, and occurred during the dose escalation period of both trials used in the current analysis, suggesting that they are not a major factor in weight loss. In particular, for the Tirzepatide dosages, the rates of nausea, diarrhea, and constipation were 31.0%–33.3%, 21.2%–23.0%, and 11.7%–17.1%, respectively; in contrast, for the Semaglutide 2.4 mg, the rates were 44.2%, 31.5%, and 23.4%.[39]

There were several advantages to this research. To find research that qualified, a thorough assessment of the literature was conducted. There were restrictions on this research as well. There were only two research that could be included in the analysis. Furthermore, aggregate data were utilized for STEP 1 since individual participant data was not accessible. The trial lengths of STEP 1 and SURMOUNT-1 were varied (72 vs. 68 weeks), although this was addressed by sensitivity analyses 2 and 5. Due to variations in how these occurrences were

gathered across studies, no formal comparisons of safety outcomes were made. Achieving a weight reduction of more than 5% was the regulatory foundation for both SURMOUNT-1 and STEP 1's key goals. Although a study of the secondary outcomes of weight reduction larger than 10%, greater than 15%, and more than 20% was beyond the scope of our investigation, this level of weight loss may no longer be clinically meaningful. The 5 mg dosage of tirzepatide was not included in the co-primary endpoint of the SURMOUNT-1 study, hence the current data do not give information on the lower dose of tirzepatide compared to Semaglutide 2.4 mg. Unmeasured confounders and other undetected variations across trials will not be taken into account by ITCs. Findings thus cannot take the place of an actual head-to-head trial.

Conclusions: In conclusion, tirzepatide 10 and 15 mg was shown to cause more weight loss and to have higher chances of attaining a 5% or more decrease in body weight compared to Semaglutide 2.4 mg in this ITC. The results of the sensitivity analysis, which took into consideration various estimands, research endpoints, and analytical strategies to reduce bias, corroborated the findings of the primary analysis. When both treatments are licensed for chronic weight management, these results may help inform clinical judgments and pharmacoeconomic analyses of the best courses of action for managing chronic weight in patients in the nonappearance of a direct head-to-head assessment.

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