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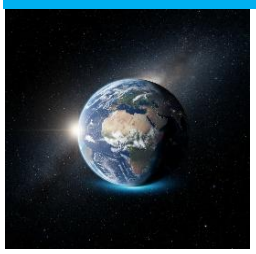

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Efficacy and Safety of Tirzepatide in the Treatment of Obesity: A Review of Current Clinical Trials

Wojciech Kijowski

Karol Marcinkowski University Hospital in Zielona Góra, Zyty 26, 65-046 Zielona Góra, Poland
https://orcid.org/0009-0006-6527-9200
kijowskiwojciech@gmail.com
Knieszko Fahim
Jan Mikulicz-Radecki University Clinical Hospital in Wrocław, Borowska 213, 50-556 Wrocław, Poland
https://orcid.org/0009-0007-6320-5758
kniecho@gmail.com

Jakub Franaszek
Independent Public Health Care Centre in Kozienice, Aleja Władysława Sikorskiego 10, 26-900 Kozienice, Poland
https://orcid.org/0009-0007-0631-9046
franaszekjakub@gmail.com
Nadia Herchi
Provincial Specialist Hospital in Wrocław, Henryka Michała Kamieńskiego 73a, 51-124 Wrocław - Karłowice, Poland
https://orcid.org/0009-0007-9952-7222
nadia.herchi@gmail.com
Martyna Jabrzyk
Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz - Central Veteran Hospital, Żeromskiego 113, 90-549 Łódź, Poland
https://orcid.org/0009-0007-7961-4986
martynajabrzyk@gmail.com
Patrycja Jarczyńska
4th Military Clinical Hospital with Polyclinic SPZOZ in Wrocław 50-981 Wrocław, Rudolfa Weigla 5, Poland
https://orcid.org/0009-0006-7249-8276
jarczynska.p@gmail.com
Mateusz Klusek
Ryszard Rzepka Hospital, Zwycięstwa Street 1, 66-100 Sulechów
https://orcid.org/0009-0009-0354-1527
matyklusek@gmail.com
Karolina Michalak
Karol Marcinkowski University Hospital in Zielona Góra, Zyty 26, 65-046 Zielona Góra, Poland
https://orcid.org/0009-0004-2572-976X
michalak.karola@gmail.com
Maciej Przybył
Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz - Central Veteran Hospital, Żeromskiego 113, 90-549 Łódź, Poland
https://orcid.org/0009-0006-1432-119X
maciejdominikprzybyl@gmail.com
Corresponding author:
Wojciech Kijowski
Karol Marcinkowski University Hospital in Zielona Góra, Zyty 26, 65-046 Zielona Góra, Poland
https://orcid.org/0009-0006-6527-9200
kijowskiwojciech@gmail.com

Abstract

Background: Obesity is a chronic disease with increasing prevalence and substantial health consequences. In recent years, advances in incretin-based pharmacotherapy have enabled greater weight loss than was achievable with earlier medications.
Aim: To evaluate the efficacy and safety of tirzepatide in the treatment of obesity based on current clinical trial evidence.

Materials and methods: A narrative review of key randomized trials from the SURMOUNT program (including SURMOUNT-1 and SURMOUNT-4), longer-term follow-up data, and meta-analyses was performed. Outcomes included mean percent weight change, clinically relevant weight-loss thresholds, durability of effect after treatment withdrawal, and adverse events.
Results: In SURMOUNT-1, tirzepatide produced a significant, dose-dependent reduction in body weight, achieving a mean weight loss of up to approximately 21% at 72 weeks compared with placebo, and a substantial proportion of participants reached ≥20% weight loss at higher doses. In SURMOUNT-4, continued therapy was essential to maintain weight loss, whereas treatment discontinuation was associated with clinically meaningful weight regain. The most common adverse events were gastrointestinal (nausea, diarrhea, vomiting), typically mild to moderate in severity.
Conclusions: Tirzepatide is an effective pharmacological option for obesity with an acceptable safety profile; however, maintenance of benefits requires long-term treatment. Further studies are needed to clarify durability of effect and long-term safety over multiple years.
Keywords: obesity; tirzepatide; weight loss; GLP-1 receptor agonist; GIP; SURMOUNT clinical trial program

Introduction

According to the World Health Organization (WHO), obesity is a chronic disease characterized by excessive accumulation of adipose tissue in the body. In adults, obesity is diagnosed using the body mass index (BMI) when BMI is ≥30 kg/m². The WHO reports that in 2022, 1 in 8 people worldwide lived with obesity, and the prevalence among adults was 16%. Moreover, between 1990 and 2022 the global prevalence of obesity among adults aged ≥18 years more than doubled [1].

Major contributing factors include environmental determinants such as unhealthy dietary habits, low physical activity, chronic positive energy balance, and long-term stress. Obesity may also be promoted by genetic and acquired conditions, as well as by certain medical treatments [2].

Obesity markedly increases the risk of cardiovascular disease, which remains the leading cause of death worldwide. It also contributes to the development of type 2 diabetes, respiratory disorders, musculoskeletal conditions, and several malignancies, including breast cancer, colorectal cancer, and endometrial cancer. Overall, obesity is associated with reduced life expectancy [2].

Given that obesity has reached epidemic proportions globally, strategies aimed at limiting its further spread and mitigating adverse consequences are of paramount importance [2].

The cornerstone of obesity management remains lifestyle modification, including dietary interventions, increased physical activity, and behavioral therapy. Reducing dietary energy intake, improving food quality, and engaging in regular physical activity can decrease body weight and improve metabolic parameters. Clinical evidence indicates that comprehensive lifestyle programs can achieve approximately 5–10% weight loss within 6 months, which is associated with meaningful reductions in cardiometabolic risk [3]. However, long-term maintenance of weight loss is challenging, and many patients experience weight regain over time [3].

When non-pharmacological interventions are insufficient, pharmacotherapy should be considered. Pharmacological treatment is recommended for patients with BMI ≥30 kg/m² or BMI ≥27 kg/m² in the presence of obesity-related comorbidities. Therapeutic goals include not only weight reduction, but also improvement of metabolic parameters and reduction of cardiometabolic risk. In recent years, obesity pharmacotherapy has evolved rapidly, and

incretin-based agents have gained particular importance due to their superior weight-loss efficacy compared with earlier therapeutic options [4–6].
Bariatric surgery is considered the most effective treatment modality for obesity and is recommended especially in patients with severe obesity or significant metabolic complications. Procedures such as sleeve gastrectomy or gastric bypass can result in substantial weight loss of approximately 30–35%, with long-term maintenance of around 25%. These interventions also improve, and in some cases induce remission of, obesity-related comorbidities. Given their invasive nature and potential complications, careful clinical evaluation and comprehensive perioperative care are required [3].
A major breakthrough in obesity pharmacotherapy has been achieved with glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide. In the STEP-1 trial, once-weekly semaglutide 2.4 mg produced a mean weight reduction of 14.9% compared with 2.4% with placebo after 68 weeks of treatment in adults with overweight or obesity without type 2 diabetes [7].
Advances in incretin-based therapy led to the development of tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. In SURMOUNT-1, tirzepatide achieved clinically meaningful weight loss exceeding 20% depending on dose [8]. By targeting two incretin pathways, tirzepatide represents the next step in obesity pharmacotherapy and may provide greater therapeutic benefit.
The aim of this review is to analyze the efficacy and safety of tirzepatide in the treatment of obesity based on current clinical trial evidence.

Mechanism of action of tirzepatide

Tirzepatide is the first agent that acts as a dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor. Activation of both receptors leads to enhanced, glucose-dependent insulin secretion and suppression of glucagon secretion, which improves glycemic control and carbohydrate metabolism [9–10]. GIP and GLP-1 receptors are also expressed in central nervous system structures involved in appetite regulation; therefore, concomitant stimulation reduces hunger and decreases energy intake [10]. In addition, tirzepatide affects the gastrointestinal tract by delaying gastric emptying, promoting earlier satiety after meals [9]. Tirzepatide has also been shown to improve insulin sensitivity and favorably affect lipid metabolism and adipose tissue biology [10]. By simultaneously influencing multiple mechanisms of energy homeostasis, tirzepatide produces substantial weight loss and improves metabolic parameters [9–10].
This complex mechanism translates into the high clinical efficacy observed in randomized trials. The most important evidence for tirzepatide in obesity comes from the SURMOUNT clinical trial program, including SURMOUNT-1 [8].

SURMOUNT clinical trial program

1. Program characteristics and study design

The SURMOUNT program comprises phase 3 randomized trials assessing the efficacy and safety of tirzepatide for the treatment of obesity and in populations with overweight and obesity-related comorbidities. The pivotal trial is SURMOUNT-1, a multicenter, randomized, double-blind, placebo-controlled study in adults with obesity or overweight without type 2 diabetes.

2. Study populations and dosing regimen

Participants were randomized to once-weekly tirzepatide at doses of 5 mg, 10 mg, or 15 mg, or to placebo, and were followed for 72 weeks.

3. Key endpoints

The primary endpoint was the percentage change in body weight from baseline. Key secondary endpoints included the proportion of participants achieving clinically meaningful weight-loss thresholds (≥5%, ≥10%, ≥15%, and ≥20%) and changes in cardiometabolic parameters [8]. This design enables a robust assessment of treatment effect versus placebo and allows analysis of dose–response relationships.

An important complement to SURMOUNT-1 is SURMOUNT-4, which provides evidence regarding maintenance of weight loss and the consequences of treatment discontinuation. SURMOUNT-4 used a randomized-withdrawal design: all participants received open-label tirzepatide for 36 weeks (with dose escalation to the maximum tolerated dose, typically 10 mg or 15 mg), and those who completed the lead-in phase were then randomized to continue tirzepatide or switch to placebo for an additional 52 weeks under double-blind conditions. The primary endpoint was the percentage change in body weight from randomization (week 36) to week 88; secondary endpoints included maintenance of prior weight loss and changes in metabolic parameters depending on continued therapy or withdrawal [11].

This study design addresses a clinically practical question regarding the durability of weight-loss effects and the risk of weight regain after treatment discontinuation.

Additional evidence on longer-term outcomes and incident type 2 diabetes risk is provided by a publication evaluating tirzepatide for obesity treatment and diabetes prevention over 176 weeks. The study assessed maintenance of weight loss and the incidence of type 2 diabetes in tirzepatide versus placebo groups, extending the perspective from short-term efficacy to metabolic and preventive outcomes [12]. A systematic review and meta-analysis summarizes the magnitude of weight loss and adverse-event profile across trials, enabling a consolidated appraisal of efficacy and safety across populations (obesity and/or type 2 diabetes) and doses [13].

The key features of the major SURMOUNT studies are summarized in Table 1.

Study	Design	Population	Intervention / comparator	Follow-up	Primary endpoint(s)
SURMOUNT-1	Randomized, double-blind, placebo-controlled	Obesity or overweight, without T2D	Tirzepatide 5/10/15 mg once weekly vs placebo	72 weeks	Percent change in body weight from baseline; thresholds (≥5%, ≥10%, ≥15%, ≥20%)

SURMOUNT-4	Randomized withdrawal: 36-week lead-in + 52-week DB phase	Obesity or overweight, without T2D (after tirzepatide lead-in)	Continue tirzepatide vs switch to placebo	36-week lead-in + 52-week DB (88 weeks total)	Change in body weight from week 36 to 88; maintenance of weight loss
176-week follow-up (obesity + diabetes prevention)	Longer-term, placebo-controlled follow-up	Obesity or overweight (long-term)	Tirzepatide 5/10/15 mg once weekly vs placebo	176 weeks	Maintenance of weight reduction; incidence of T2D

Table 1. Key characteristics of SURMOUNT clinical trials. Study design, population, intervention/comparator, follow-up, and primary endpoints for SURMOUNT-1, SURMOUNT-4, and the 176-week follow-up are shown. **Abbreviations:** T2D, type 2 diabetes; DB, double-blind. **Sources:** [8,11,12].

Clinical efficacy of tirzepatide

1. Weight reduction (SURMOUNT-1)

In SURMOUNT-1, tirzepatide demonstrated significant, dose-dependent efficacy in reducing body weight in adults with obesity or overweight without type 2 diabetes. At 72 weeks, the mean percentage change in body weight was −15.0% in the 5 mg group, −19.5% in the 10 mg group, and −20.9% in the 15 mg group, compared with −3.1% with placebo (all comparisons statistically significant) [8]. These findings indicate greater weight loss with higher doses and a progressive effect over time.

Key outcomes for weight reduction in SURMOUNT-1 are presented in Table 2.

Group	**Mean percent change in body weight (72 weeks)**	**Participants with ≥20% weight reduction**
Tirzepatide 5 mg	−15.0%	30.0%
Tirzepatide 10 mg	−19.5%	50.1%
Tirzepatide 15 mg	−20.9%	56.7%
Placebo	−3.1%	3.1%

Table 2. Tirzepatide efficacy for weight reduction in SURMOUNT-1 (72 weeks). Mean percent change in body weight from baseline and the proportion of participants achieving ≥20% weight reduction. **Source:** [8].

From a practical perspective, these data are clinically important for two reasons. First, the magnitude of weight loss approaches that observed with bariatric interventions in a subset of patients, representing a qualitative advance in obesity pharmacotherapy. Second, the dose–response relationship underscores the need for appropriate dose escalation and individualized treatment based on tolerability and expected benefit [8]. In SURMOUNT-1, prespecified cardiometabolic parameters (including glycemic indices, lipids, and blood pressure) also improved, highlighting benefits beyond weight loss alone [8]. From a review perspective, it is

worth noting at this point that the observed metabolic changes are consistent with the drug's mechanism of action as a dual GIP and GLP-1 receptor agonist.
Longer-term durability is supported by the 176-week analysis, which demonstrated sustained, clinically meaningful weight reduction with tirzepatide: −12.3% (5 mg), −18.7% (10 mg), and −19.7% (15 mg), compared with −1.3% with placebo [12]. Although some patients may reach a plateau and experience partial attenuation over time, treatment enabled long-term maintenance of clinically important weight loss, particularly at higher doses [12].
Additional evidence comes from other SURMOUNT trials. SURMOUNT-3 evaluated tirzepatide in adults with obesity or overweight after an intensive lifestyle intervention, enabling assessment in a setting closer to routine clinical practice [14]. SURMOUNT-2 included participants with obesity and type 2 diabetes, providing efficacy data in a population at high metabolic risk [15].

2. Proportion of participants achieving weight-loss thresholds

In obesity trials, clinically informative outcomes include not only mean weight change but also the proportions of participants achieving prespecified thresholds, as these correlate with improvements in metabolic risk. In SURMOUNT-1, the proportion achieving ≥5% weight reduction was high: 85% (5 mg), 89% (10 mg), and 91% (15 mg), compared with 35% with placebo [8]. This finding indicates that the majority of patients treated with tirzepatide achieve at least the minimally clinically meaningful threshold for weight loss.
Higher thresholds are particularly relevant clinically. In SURMOUNT-1, ≥20% weight reduction was achieved by 50% of participants receiving 10 mg and 57% receiving 15 mg, compared with 3% with placebo [8]. These findings indicate that, at higher doses, a substantial proportion of patients can achieve weight reductions that were rarely attainable with earlier pharmacotherapies. In clinical practice, this suggests that substantial weight reduction can be achieved in a considerable proportion of patients without the need for surgical intervention; however, decisions to escalate the dose should take treatment tolerability and the risk of adverse events into account [8].
A meta-analysis of tirzepatide trials confirms a dose-dependent increase in the likelihood of achieving clinically meaningful thresholds. The analysis demonstrated superiority over placebo for ≥5%, ≥10%, and ≥15% thresholds, supporting the consistency of effect across study populations (obesity and/or type 2 diabetes) and doses [13]. Meta-analytic synthesis is particularly useful in a review article because it demonstrates the consistency of the effect across different studies and doses.

3. Maintenance of effect and consequences of discontinuation (SURMOUNT-4)

Maintaining weight loss remains a key challenge in obesity management. SURMOUNT-4 directly addressed whether continued treatment is required to sustain benefit. After 36 weeks of open-label tirzepatide, participants achieved a mean weight reduction of 20.9%. From week 36 to 88, those continuing tirzepatide experienced an additional mean change of −5.5%, whereas those switched to placebo regained 14.0% (between-group difference −19.4 percentage points) [11]. These results clearly indicate that discontinuation of tirzepatide is associated with marked weight regain, whereas continued therapy allows maintenance and further enhancement of weight loss.
Maintenance of weight reduction and weight regain after tirzepatide discontinuation in SURMOUNT-4 are shown in Table 3.

Stage / outcome	Continued tirzepatide	Switched to placebo
Weight reduction after 36-week lead-in	20.9%	20.9%
Change in body weight from week 36 to 88	−5.5%	+14.0%
Total weight reduction from baseline to week 88	−25.3%	−9.9%
Maintained ≥80% of weight loss at week 88	89.5%	16.6%

Table 3. Maintenance of weight reduction with continuation versus discontinuation of tirzepatide in SURMOUNT-4. Weight change during the randomized phase (weeks 36–88), total weight reduction from baseline to week 88, and the proportion of participants maintaining ≥80% of weight loss achieved during lead-in are shown. The 20.9% value applies to the overall cohort after lead-in (prior to randomization). **Source:** [11].

An important aspect of SURMOUNT-4 is the data on the maintenance of the weight loss achieved during the earlier phase of treatment. At week 88, 89.5% of participants continuing tirzepatide maintained at least 80% of weight loss achieved during lead-in, compared with 16.6% with placebo [11]. Total mean weight reduction from baseline to week 88 was 25.3% with continued tirzepatide and 9.9% with placebo [11]. These findings are clinically important because they support the concept of obesity as a chronic disease requiring long-term management and suggest that—similar to many other chronic conditions—discontinuation of effective therapy is associated with symptom recurrence.

In addition, SURMOUNT-4 showed that continued therapy was associated with favorable cardiometabolic changes compared with treatment discontinuation, including improvements in glycemic parameters, lipid levels, and blood pressure [11]. Moreover, longer-term follow-up in the obesity treatment and diabetes prevention study demonstrated a markedly lower incidence of type 2 diabetes in participants receiving tirzepatide compared with placebo (1.3% vs 13.3%), suggesting that treatment benefits may extend beyond weight loss alone to include metabolic risk reduction in high-risk individuals [12].

Safety

1. Gastrointestinal adverse events

The safety profile of tirzepatide is dominated by gastrointestinal adverse events typical of incretin-based therapies. In SURMOUNT-1, the most frequently reported adverse events were gastrointestinal, generally mild to moderate, and occurred predominantly during dose escalation [8]. According to the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC), in individuals without type 2 diabetes, gastrointestinal disorders were more common with tirzepatide than with placebo (approximately 56–61% vs 30%); the most common events were nausea (approximately 25–33% vs 9.5%) and diarrhea (approximately 19–23% vs 7.3%) [16]. During the lead-in phase of SURMOUNT-4, adverse events were reported by 81.0% of participants; nausea (35.5%), diarrhea (21.1%), constipation (20.7%), and vomiting (16.3%) were most common, and the incidence of new gastrointestinal events declined over time [11].

A meta-analysis of clinical trials confirms that tirzepatide is less well tolerated than placebo, with differences driven mainly by gastrointestinal symptoms; adverse events were more frequent in the tirzepatide groups, and the risk of treatment discontinuation increased with higher doses [13]. Accordingly, gradual dose escalation, patient education, and symptomatic measures (e.g., smaller meals and adequate hydration) are essential. EMA documentation notes that gastrointestinal events may lead to dehydration and secondary deterioration of renal function; patients should be counseled to prevent fluid loss, particularly in the presence of severe nausea, vomiting, or diarrhea [16].

2. Treatment discontinuation and tolerability

In SURMOUNT-1, discontinuation due to adverse events occurred in 4.3% (5 mg), 7.1% (10 mg), and 6.2% (15 mg) of participants, compared with 2.6% with placebo [8]. These data indicate that although treatment tolerability is generally acceptable, the risk of discontinuation may increase at higher doses, primarily due to gastrointestinal symptoms. EMA product information indicates that permanent discontinuation due to gastrointestinal events was higher with tirzepatide (approximately 3.0–6.6%) than with placebo (0.4%), emphasizing the importance of gastrointestinal tolerability in long-term therapy [16].

SURMOUNT-4 provides additional insight into tolerability over a longer horizon: during the lead-in phase, discontinuations due to adverse events occurred in 7.0% of participants (mainly for gastrointestinal reasons), whereas during the randomized double-blind phase the discontinuation rate was low—1.8% in the continued-tirzepatide group and 0.9% in the placebo group [11]. These findings support the observation that some adverse events occur early (particularly during dose escalation) and that, once a maintenance dose is achieved, treatment tolerability improves in many patients.

3. Long-term safety and limitations of current evidence

Available evidence suggests that a similar safety profile is maintained with longer follow-up. In the long-term analysis (176 weeks) of obesity treatment and type 2 diabetes prevention, the most common adverse events (apart from COVID-19) were gastrointestinal, were generally mild to moderate in severity, and occurred mainly during the first weeks of dose escalation; no new safety signals were reported [12]. At the same time, it should be emphasized that despite progressively longer follow-up in clinical trials, large controlled data extending beyond 5 years are still lacking, which limits a comprehensive assessment of long-term safety in chronically treated populations.

In SURMOUNT-4, serious adverse events were uncommon and occurred at similar frequencies across treatment groups during the double-blind phase; no confirmed cases of pancreatitis were reported, and gallbladder-related events occurred sporadically [11]. EMA documentation highlights selected clinically relevant safety considerations, including the risk of dehydration in the setting of gastrointestinal symptoms, caution in patients with severe gastrointestinal disease (e.g., severe gastroparesis), and the risk of hypoglycemia when used in combination with insulin or sulfonylureas [16]. From a clinical practice perspective, this supports the need for individualized treatment, monitoring of tolerability during dose escalation, and further studies with longer follow-up and real-world evidence.

Discussion

1. Clinical relevance of weight reduction

The weight reduction achieved with tirzepatide in clinical trials is clinically meaningful. Weight loss of 5–10% achieved through comprehensive lifestyle interventions is associated with improved metabolic parameters and reduced cardiometabolic risk [3]. SURMOUNT-1 demonstrated mean weight reductions of −15.0% to −20.9% (vs −3.1% with placebo) at 72 weeks, far exceeding minimally clinically important thresholds [8]. Additionally, many participants achieved very large weight reductions (e.g., ≥20% at higher doses), which may translate into meaningful improvements in health status and quality of life [8]. Durability is supported by the 176-week follow-up showing sustained weight reduction versus placebo [12]. A key implication is that obesity pharmacotherapy should be considered chronic treatment. In SURMOUNT-4, withdrawal after substantial weight loss led to marked regain, whereas continued therapy maintained and further improved weight reduction [11]. This observation is consistent with obesity as a chronic disease, with biological mechanisms that promote weight regain after weight loss. Clinically, patients should be prepared for long-term therapy and monitored for tolerability during dose escalation [11,16].

2. Comparison with other anti-obesity medications

Tirzepatide fits within the broader trend of incretin-based obesity pharmacotherapy. Recent narrative reviews have emphasized its growing role in obesity management and its potential position in treatment algorithms for patients at high metabolic risk [17–18]. In STEP-1, once-weekly semaglutide 2.4 mg achieved a mean weight reduction of 14.9% at 68 weeks compared with 2.4% with placebo, representing a major advance over earlier pharmacotherapies [7]. In contrast, SURMOUNT-1 indicates that tirzepatide can deliver even greater mean weight loss in a dose-dependent manner [8]. Although direct comparative evidence remains limited, indirect comparisons provide useful context. A systematic review with network meta-analysis of randomized anti-obesity drug trials identified both semaglutide and tirzepatide among the most effective agents, typically achieving >10% total body weight loss, and supported individualized treatment selection based on efficacy and tolerability [19]. Importantly, this analysis highlighted gastrointestinal adverse events and treatment discontinuations as key determinants of the overall benefit–risk balance in routine practice [19]. Moreover, in SURMOUNT-5 (a head-to-head comparison), tirzepatide produced greater weight reduction than semaglutide at 72 weeks, strengthening conclusions drawn from indirect comparisons [20]. Real-world evidence is also emerging, although it should be interpreted cautiously because of potential confounding and bias. In an ambulatory-care observational study comparing tirzepatide with semaglutide, tirzepatide was associated with greater weight loss at 6 months (mean 5.3% vs 2.7%), with a more pronounced difference among individuals without diabetes [21]. These findings are consistent with the direction observed in randomized trials; however, the shorter follow-up and potential differences in dose titration or adherence warrant cautious interpretation [21].

Across clinical trials, gastrointestinal adverse events are the main safety consideration for tirzepatide. In SURMOUNT-1, gastrointestinal symptoms were the most common adverse events and were generally mild to moderate, occurring more frequently during dose escalation [8]. Meta-analytic evidence similarly indicates that gastrointestinal adverse events dominate the

safety profile and that discontinuation risk may increase with higher doses [13]. Regulatory product information (SmPC) emphasizes monitoring for dehydration in patients with severe gastrointestinal symptoms and caution in selected clinical situations [16]. Overall, with appropriate patient education, gradual dose escalation, and symptomatic management, tirzepatide is acceptable for many patients; nevertheless, tolerability remains a central factor influencing long-term continuation of therapy [8,13,16].

3. Limitations of the evidence and perspectives for further research

The limitations of the available evidence should also be considered. First, despite follow-up data extending to 176 weeks, randomized evidence covering very long periods (>5 years) is still lacking, which limits a comprehensive assessment of long-term safety and durability of effect [12]. Second, treatment costs and the availability of reimbursement may restrict the use of tirzepatide in routine practice, irrespective of clinical efficacy. Third, although real-world evidence is increasing, it remains relatively limited, often covers shorter observation periods, and requires confirmation in larger populations, including evaluation under real-life dose-escalation schedules and adherence patterns [21]. Finally, the limited number of direct comparative trials between currently available anti-obesity medications means that some comparative conclusions still rely on indirect analyses, reinforcing the need for additional head-to-head studies [19]. In the case of semaglutide, longer-term data are available from the two-year STEP 5 trial, whereas for tirzepatide randomized trial data beyond 5 years are still unavailable [22].

In summary, tirzepatide is an effective pharmacological option for obesity, enabling substantial, clinically meaningful weight reduction and supporting maintenance of weight loss with continued treatment [8,11]. Available evidence suggests high effectiveness compared with other anti-obesity medications; however, direct comparisons remain limited and further studies are warranted [19]. From a practical perspective, gastrointestinal tolerability and the need for chronic therapy remain key considerations, alongside the need to accumulate longer-term observational evidence in real-world settings [11,13,16,21].

Conclusions

Tirzepatide demonstrates high efficacy in reducing body weight in adults with obesity, significantly outperforming placebo and enabling achievement of clinically meaningful weight-loss thresholds.

The magnitude of weight reduction is dose-dependent, with higher doses producing greater weight loss.

The safety profile of tirzepatide is acceptable; adverse events are predominantly gastrointestinal and are most often mild to moderate.

Maintenance of weight loss requires continued therapy; discontinuation is associated with clinically meaningful weight regain.

Further long-term studies and real-world evidence are needed to better define durability of effect and long-term safety.

Supplementary materials:

Not applicable.

Author’s contribution:

Conceptualization: Wojciech Kijowski, Jakub Franaszek, Maciej Przybył; methodology: Wojciech Kijowski, Mateusz Klusek, Karolina Michalak; software: Knieszko Fahim, Mateusz Klusek; validation: Wojciech Kijowski, Martyna Jabrzyk, Patrycja Jarczyńska; formal analysis: Wojciech Kijowski, Knieszko Fahim, Maciej Przybył; investigation: Wojciech Kijowski, Nadia Herchi, Martyna Jabrzyk; resources: Jakub Franaszek, Karolina Michalak; data curation: Wojciech Kijowski, Patrycja Jarczyńska, Nadia Herchi; writing – original draft preparation: Wojciech Kijowski, Knieszko Fahim, Jakub Franaszek; writing – review and editing: Wojciech Kijowski, Maciej Przybył, Martyna Jabrzyk, Karolina Michalak; visualization: Mateusz Klusek, Patrycja Jarczyńska; supervision: Wojciech Kijowski, Maciej Przybył; project administration: Wojciech Kijowski, Nadia Herchi.

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References

1. World Health Organization. Obesity and overweight [Internet]. Geneva: World Health Organization; 2025 Dec 8 [cited 2026 Mar 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Ahmed SK, Mohammed RA. Obesity: Prevalence, causes, consequences, management, preventive strategies and future research directions. Metabol Open. 2025;27:100375. PMID: 41041606 DOI: 10.1016/j.metop.2025.100375 https://doi.org/10.1016/j.metop.2025.100375
3. Idris I, Anyiam O. The latest evidence and guidance in lifestyle and surgical interventions to achieve weight loss in people with overweight or obesity. Diabetes Obes Metab. 2025;27(Suppl 2):20-34. PMID: 40026042 DOI: 10.1111/dom.16296 https://doi.org/10.1111/dom.16296
4. Tchang BG, Aras M, Kumar RB, Aronne LJ. Pharmacologic Treatment of Overweight and Obesity in Adults. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- [updated 2024 Aug 20; cited 2026 Mar 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279038/
5. Woch B, Bereza D, Sokołowska K, Kulak M, Moreau I, Polańska P, et al. Pharmacological treatment of obesity: an overview of different groups of anti-obesity drugs available in Poland. J Educ Health Sport. 2024;58:48-59. DOI: 10.12775/JEHS.2024.58.004 https://doi.org/10.12775/JEHS.2024.58.004
6. Chakhtoura M, Haber R, Ghezzawi M, Rhayem C, Tcheroyan R, Mantzoros CS. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. EClinicalMedicine. 2023;58:101882. PMID: 36992862 DOI: 10.1016/j.eclinm.2023.101882 https://doi.org/10.1016/j.eclinm.2023.101882
7. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989-1002. PMID: 33567185 DOI: 10.1056/NEJMoa2032183 https://doi.org/10.1056/NEJMoa2032183
8. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-216. PMID: 35658024 DOI: 10.1056/NEJMoa2206038 https://doi.org/10.1056/NEJMoa2206038

9. Singh A, Ahmad R, Chowdhury K, Narwaria M, Haque M. Tirzepatide and obesity: a narrative review. Adv Hum Biol. Published online 2025 Dec 6. DOI: 10.4103/aihb.aihb_244_25
https://doi.org/10.4103/aihb.aihb_244_25
10. Galindo RJ, Cheng AYY, Longuet C, Ai M, Coskun T, Malik R, et al. Insights into the mechanism of action of tirzepatide: a narrative review. Diabetes Ther. 2026;17(1):19-40. PMID: 41196501 DOI: 10.1007/s13300-025-01804-w
https://doi.org/10.1007/s13300-025-01804-w
11. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. JAMA. 2024;331(1):38-48. PMID: 38078870 DOI: 10.1001/jama.2023.24945
https://doi.org/10.1001/jama.2023.24945
12. Jastreboff AM, le Roux CW, Stefanski A, Aronne LJ, Halpern B, Wharton S, et al. Tirzepatide for obesity treatment and diabetes prevention. N Engl J Med. 2025;392(10):958-971. PMID: 39536238 DOI: 10.1056/NEJMoa2410819
https://doi.org/10.1056/NEJMoa2410819
13. Tian Q, Song Y, Deng Y, Lin S. Efficacy and safety of tirzepatide for weight loss in patients with obesity or type 2 diabetes: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2025;16:1593134. PMID: 40747302 DOI: 10.3389/fendo.2025.1593134
https://doi.org/10.3389/fendo.2025.1593134
14. Wadden TA, Chao AM, Machineni S, Kushner R, Ard J, Srivastava G, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023;29(11):2909-2918. PMID: 37840095 DOI: 10.1038/s41591-023-02597-w
https://doi.org/10.1038/s41591-023-02597-w
15. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402(10402):613-626. PMID: 37385275 DOI: 10.1016/S0140-6736(23)01200-X
https://doi.org/10.1016/S0140-6736(23)01200-X
16. European Medicines Agency. Mounjaro (tirzepatide): EPAR - product information (SmPC) [Internet]. Amsterdam: European Medicines Agency; 2026 Feb 26 [cited 2026 Mar 14].

Available from: https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf

17. Stachyra B, Wolanin M, Stawikowski C, Zielonka B, Osińska A, Wolanin I, et al. Tirzepatide – a novel dual GLP-1 and GIP receptor agonist used in pharmacotherapy of obesity: a literature review. J Educ Health Sport. 2023;18(1):23-33. DOI: 10.12775/JEHS.2023.18.01.003 https://doi.org/10.12775/JEHS.2023.18.01.003
18. Doryń A, Woźniak K, Jung M, Jung M, Hedesz P, Warzycka K, et al. Will Tirzepatide become a game-changer in the pharmacological treatment of obesity? - literature review. J Educ Health Sport. 2024;71:49544. DOI: 10.12775/JEHS.2024.71.49544 https://doi.org/10.12775/JEHS.2024.71.49544
19. McGowan B, Ciudin A, Baker JL, Busetto L, Dicker D, Frühbeck G, et al. A systematic review and meta-analysis of the efficacy and safety of pharmacological treatments for obesity in adults. Nat Med. 2025;31(10):3317-3329. PMID: 41039116 DOI: 10.1038/s41591-025-03978-z https://doi.org/10.1038/s41591-025-03978-z
20. Aronne LJ, Bade Horn D, le Roux CW, Ho W, Falcon BL, Gomez Valderas E, et al. Tirzepatide as compared with semaglutide for the treatment of obesity (SURMOUNT-5). N Engl J Med. 2025;393(1):26-36. PMID: 40353578 DOI: 10.1056/NEJMoa2416394 https://doi.org/10.1056/NEJMoa2416394
21. Trinh H, Donovan A, McAdam-Marx C. Real-world effectiveness of tirzepatide versus semaglutide for weight loss in overweight or obese patients in an ambulatory care setting. Diabetes Obes Metab. 2025;27(6):3523-3525. PMID: 40116184 DOI: 10.1111/dom.16343 https://doi.org/10.1111/dom.16343
22. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083-2091. PMID: 36216945 DOI: 10.1038/s41591-022-02026-4 https://doi.org/10.1038/s41591-022-02026-4