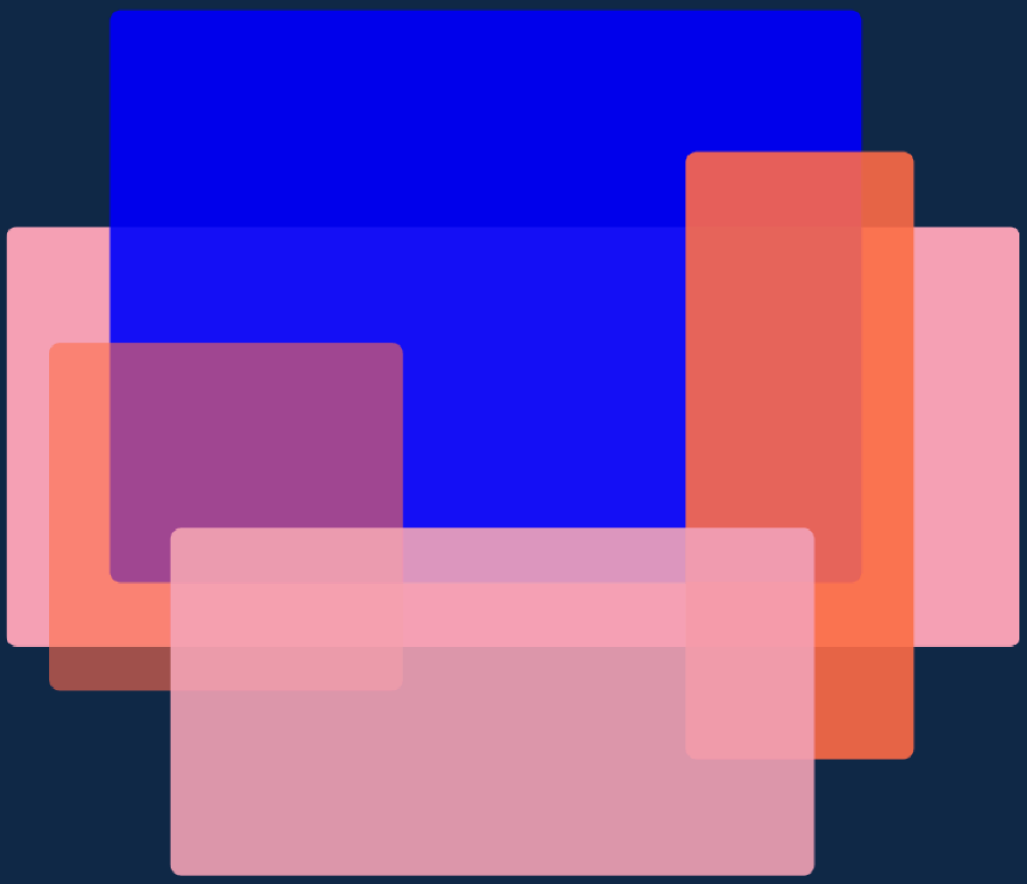
Blueprint
by nesta

Blueprint for halving obesity: rapid review

Effectiveness of the weight-loss medication tirzepatide on clinical outcomes in obesity



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Contents

Summary table

Title	Tirzepatide Once Weekly for the Treatment of Obesity (SURMOUNT-1)	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
Authors	Jastreboff et al. (2022)	Garvey et al. (2023)
Type of study	Phase 3 double-blind, randomised, controlled trial	Phase 3 double-blind, randomised, controlled trial
Outcome variable	Percentage change in weight from baseline	Percentage change in weight from baseline
Treatment	5mg, 10mg or 15mg subcutaneous tirzepatide taken once weekly over a 72-week period (alongside a lifestyle intervention)	10mg or 15mg subcutaneous tirzepatide taken once weekly over a 72-week period (alongside a lifestyle intervention)
Control	Placebo injection (alongside a lifestyle intervention)	Placebo injection (alongside a lifestyle intervention)
Magnitude of effect (Adults)	Mean percentage weight change (at 72 weeks): - Placebo: -3.1% [95% CI: -4.3 to -1.9] - 5mg: -15.0% [95% CI: -15.9 to -14.2] - 10mg: -19.5% [95% CI: -20.4 to -18.5]	Least-squares mean percentage weight change (at 72 weeks): - Placebo: -3.2% [SE 0.5] - 10mg: -12.8% [SE 0.6] - 15mg: -14.7% [SE 0.5] Overall, we take the mean effect size of 13.8% as the weight loss

	- 15mg: -20.9% [95% CI: -21.8 to -19.9] We take the mean effect size of 18.5% as the weight loss experienced by those living with obesity and receiving treatment.	experienced by those living with obesity and receiving treatment.
Magnitude of effect (Children)	n/a	n/a
Notes	For modelling the impact of this policy, both reviews were used (as highlighted in green). The effect sizes from Jastreboff et al. (2022) were used to model the effect of tirzepatide on individuals without type 2 diabetes, and those from Garvey et al. (2023) for those living with type 2 diabetes.	

Rapid umbrella review

Background

Obesity rates have nearly doubled in recent decades and it is estimated that nearly 2 billion people are living with obesity worldwide. Excess weight is a significant risk factor for health problems (eg, certain cancers, high blood pressure, type 2 diabetes) and premature death from non-communicable diseases.

Although lifestyle modification interventions (eg, diet modification, physical activity) are the mainstay for the treatment of obesity, pharmaceutical interventions are becoming increasingly important in the clinical management of obesity. In recent years, the NHS has approved the use of various weight-loss medications – orlistat, liraglutide, and semaglutide – known as GLP-1s.

In 2024, the National Institute for Health and Care Excellence (NICE) published guidance on an NHS rollout of another type of weight-loss medication – Tizepatide (known under the brand name Mounjaro) – which would be offered alongside a reduced-calorie diet and increased physical activity. Tirzepatide is a glucose-lowering medication that stimulates both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonists. It increases insulin sensitivity and secretion, suppresses glucagon secretion, and slows gastric emptying.

Objectives

To summarise the evidence referenced by the 2024 NICE guidance on the impact of the weight-loss medication tirzepatide on energy intake or body weight.

Methods

Other Blueprint policies (and associated rapid reviews) have been underpinned by a literature search for the best available evidence for that policy. However, this rapid review does not follow this methodology as the present policy reflects an existing

implementation plan. Specifically, the policy models the impact of an NHS rollout of the weight-loss medication tirzepatide, as proposed in the 2024 NICE guidance.

Therefore, rather than conducting literature searches, we instead reviewed the evidence on which the NICE guidance is based.

Results

Two studies were used to model the impact of tirzepatide. Jastreboff et al. (2022) was highlighted through the 2024 NICE guidance and Garvey et al. (2023) was suggested by external experts in the NHSE Prevention Team. Below is a non-exhaustive summary of the studies. Please see the original articles for full details.

Jastreboff et al. (2022). Tirzepatide Once Weekly for the Treatment of Obesity

This study, also referred to as SURMOUNT-1, evaluated the efficacy and safety of tirzepatide for weight management in adults living with obesity or overweight who did not have diabetes. Mounting evidence has shown that obesity is a risk factor for many conditions, yet once obesity is present, weight loss has increased difficulty due to counterregulatory mechanisms. Accordingly, several guidelines now recommend treatment with anti-obesity medications.

What were the study methods?

To test the effectiveness of tirzepatide on weight loss, an RCT was conducted from December 2019 to April 2022 with 2,539 participants. It encompassed 119 sites in nine countries (Argentina, Brazil, China, India, Japan, Mexico, Russia, Taiwan, and the USA) with the intent of making findings generalisable globally.

Participants were randomly assigned to one of four treatment arms (1:1:1:1 ratio) to receive tirzepatide at a dose of 5mg, 10mg, or 15mg or placebo for a planned 72-week treatment period, with a dose-escalation period of up to 20 weeks. In addition, participants had a lifestyle intervention. Treatment randomisation was stratified by country, sex, and the presence or absence of prediabetes.

To be eligible for the trial, participants needed to be an adult with a BMI of 30 kg/m^2 or more, or a BMI of 27 kg/m^2 or more with at least one weight-related complication (not including type 2 diabetes), and who reported one or more unsuccessful dietary

effort to lose weight. Key exclusion criteria were diabetes, a change in body weight of more than 5 kg within 90 days before screening, previous or planned surgical treatment for obesity, and treatment with a medication that promotes weight loss within 90 days before screening.

The primary outcomes were the percentage change in body weight and a weight reduction of 5% or more from baseline to week 72. Secondary endpoints included: additional benchmarks of percentage weight reduction; weight change at week 20; change in waist circumference; systolic blood pressure; fast insulin; lipid levels; and the physical function score on the 36-Item Short Form Health Survey (SF-36).

What did the study find?

Overall, 86% of participants completed the trial, with the proportion increasing to approximately 90% across the tirzepatide groups.

The trial found that all three doses of tirzepatide demonstrated substantial and sustained weight reduction in adults with obesity. The mean percentage change in weight at week 72 was −15.0% (95% CI: −15.9 to −14.2) with a 5mg weekly dose of tirzepatide, −19.5% (95% CI: −20.4 to −18.5) with a 10mg dose, and −20.9% (95% CI: −21.8 to −19.9) with a 15mg dose. The control group (receiving a placebo with a lifestyle intervention) experienced a mean change of −3.1% (95% CI: −4.3 to −1.9). For our model, we took the mean effect size between the three dose sizes of 18.5% weight loss experienced. This is because the NICE and NHS England guidelines indicate that patients may be titrated up to the maximum dose based on their tolerance. Furthermore, it was unlikely that all patients eligible for the drug would titrate to the maximum dose, so taking the mean of the three doses ensured that our modelling would not overestimate the impact based on a higher dosage.

The most common adverse events experienced were gastrointestinal, occurring primarily during dose escalation. Adverse events caused treatment discontinuations in 4.3%, 7.1%, and 6.2% for participants with 5mg, 10mg, and 15mg of tirzepatide, respectively, and 2.6% with placebo.

While the large sample size, high completion rate and global nature make the trial findings largely generalisable, it is important to note that the enrolled participants

may represent a population with a greater commitment to weight management efforts than the general population.

Garvey et al. (2023). Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes

This study, also referred to as SURMOUNT-2, evaluated the efficacy and safety of tirzepatide for weight management in people living with obesity and type 2 diabetes. Weight management is a recommended key component of type 2 diabetes treatment, but anti-obesity medications have generally been found to be less efficacious in people with type 2 diabetes.

What were the study methods?

An RCT was conducted to test the effectiveness of tirzepatide on weight loss in people with type 2 diabetes between March 2021 and April 2023. The study took place across seven countries: Argentina, Brazil, India, Japan, Russia, Taiwan, and the USA.

Participants underwent a planned 72-week treatment period that included a dose-escalation period of 12-20 weeks (dependent on the dose of tirzepatide). They were randomly assigned to one of three treatment arms (1:1:1 ratio) of 10mg, 15mg and placebo with allocation via a computer-generated random sequence. A lifestyle intervention was also provided alongside this.

To be eligible for the trial, participants needed to be an adult with a BMI of 27 kg/m^2 or more with a type 2 diabetes diagnosis and a glycated haemoglobin of 7-10% (on stable therapy, either diet and exercise alone or oral antihyperglycaemic medication, for at least 3 months before screening). Key exclusion criteria included a change in body weight of more than 5 kg within 3 months before screening, previous or planned surgical treatment for obesity, and treatment with certain anti-obesity medications. Further, people treated with any injectable therapy for type 2 diabetes (including insulin) within 3 months of screening were excluded from participation.

The primary outcomes were the percentage change in body weight and a weight reduction of 5% or more from baseline to week 72. Secondary endpoints included: additional benchmarks of percentage weight reduction; weight change at week

20; change in waist circumference; systolic blood pressure; fast insulin; lipid levels; the physical function score on the 36-Item Short Form Health Survey (SF-36); and change in glycated haemoglobin.

What did the study find?

Of the 1,514 screened individuals for the trial, over a third were not enrolled, leaving a total of 938 participants. Most (56%) of the individuals who were rejected did not meet diabetes-related eligibility criteria.

Overall, 92% of participants completed the study, with the treatment groups having slightly higher attrition rates than the placebo group.

In this trial, both doses of tirzepatide were found to provide substantial and clinically meaningful weight loss. The least-squares mean percent weight change at week 72 with tirzepatide 10mg and 15mg was -12.8% (SE 0.6) or -12.9 kg, and -14.7% (SE 0.5) or -14.8 kg, respectively, and -3.2% (0.5) or -3.2 kg with placebo. For our model, we took the mean effect size between the two dose sizes of 13.8% weight loss experienced.

The most frequently reported adverse events were gastrointestinal disorders. Treatment discontinuations due to adverse events occurred in 4%, 7% and 4% respectively in the tirzepatide 10mg, tirzepatide 15mg and placebo groups.

A potential limitation of this trial was that tirzepatide 5mg, an approved dose for treating type 2 diabetes that safely produced significant weight reduction in previous studies in participants with and without type 2 diabetes, was not evaluated. However, the study's global nature and large sample size make results relatively generalisable. It would be of interest to study even longer-term effects of tirzepatide treatment and what occurs following cessation of treatment.