



Tirzepatide and the Weight-Regain Question: A Narrative Review of What Happens When Treatment Stops

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Abstract

The question of what happens when an incretin-based weight treatment is stopped has been answered directly by a randomised withdrawal trial. After 36 weeks of open-label tirzepatide, during which mean weight fell by 20.9 per cent, 670 participants were randomised either to continue or to switch to placebo for a further 52 weeks. Those who continued lost a further 5.5 per cent; those switched to placebo gained 14.0 per cent, a difference of 19.4 percentage points. At week 88, 89.5 per cent of the continuing group had maintained at least 80 per cent of their lead-in weight loss against 16.6 per cent of those withdrawn. Two qualifications belong with those figures. The placebo group was still 9.9 per cent below its starting weight at the end, so withdrawal did not simply undo the treatment; and regain was highly variable, with 54 of 308 withdrawn participants regaining less than a quarter of what they had lost while 74 regained three quarters or more. This review sets out what the trial establishes and what it leaves open.

Keywords: Tirzepatide; Weight regain; Randomised withdrawal; Obesity pharmacotherapy; Treatment continuation

Introduction

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, and in its pivotal obesity trial produced mean weight reduction of around 20 per cent at 72 weeks [1,2]. That magnitude moved pharmacological treatment of obesity into a range previously reached only by surgery [3,21,32]. The same agent has since shown benefit in type 2 diabetes, heart failure with preserved ejection fraction, obstructive sleep apnoea and diabetes prevention [16,17,27,28,29], and has been compared directly with semaglutide [19,33].

A separate question follows immediately from it. If the effect depends on continued exposure, then stopping returns the patient towards where they began, and the treatment is not a course but an indefinite commitment [4,5]. Earlier agents showed exactly that pattern, with weight regain after withdrawal reported across drug classes over more than two decades [6,7,24,25]. Physiological adaptations that favour regain persist

long after the loss itself, and intensive lifestyle programmes show the same trajectory [23,25].

A randomised withdrawal design answers the question directly rather than by inference. This review examines what that trial found, what its post hoc analysis adds about the variation between individuals, and what neither can settle.

Eligibility: Studies were included if they reported weight or cardiometabolic outcomes after planned or observed cessation of treatment, or characterised the variability of that response. Trials of continued treatment are cited as the comparator and are identified as such.

Material and Methods

Search strategy: PubMed and the archives of the major obesity, endocrinology and general medical journals were searched for studies of weight change after withdrawal of incretin-based therapy. Search terms combined tirzepatide and semaglutide with withdrawal, discontinuation, weight regain, maintenance and randomised withdrawal. Reference lists of the principal trial reports [1,8] were screened by hand for related analyses.

Data extraction and handling: Design, population, the randomisation point, follow-up duration and the reported estimate were extracted as published. The reference point for every weight figure is stated, because change from randomisation and change from study entry describe different quantities in a withdrawal design and conflating them misrepresents the result. This review reports trial findings and makes no dietary, caloric or exercise recommendations. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The design: The trial ran at 70 sites across four countries. Adults with a body mass index of 30 kg/m2 or above, or 25 to under 30 with at least one weight-related complication, received open-label tirzepatide at a maximum tolerated dose of 10 or 15 mg weekly for 36 weeks, alongside caloric restriction and increased physical activity. Those completing the lead-in were then randomised 1:1 to continue or to receive placebo for 52 weeks (Figure 5) [1,8].

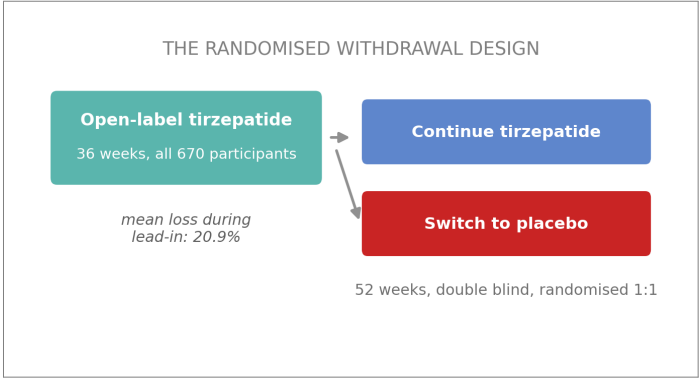


Figure 5: The randomised withdrawal design [1,8]

The participants: Six hundred and seventy participants completed the lead-in. Mean age was 48 years, 473 (71 per cent) were women, 80.1 per cent were White and mean weight was 107.3 kg. Mean weight reduction during the 36-week lead-in was 20.9 per cent [1].

The primary result: From randomisation at week 36 to week 88, mean weight changed by -5.5 per cent among those continuing tirzepatide and by +14.0 per cent among those switched to placebo, a difference of -19.4 percentage points (95% CI -21.2 to -17.7, $p < 0.001$) (Figure 1) [1]. Continued

treatment therefore did not merely hold the loss; it added to it.

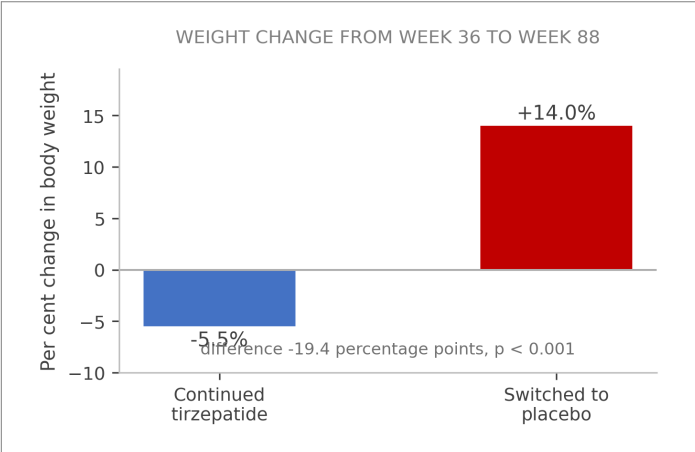


Figure 1: Weight change from randomisation at week 36 to week 88 [1]

Maintenance of the initial loss: At week 88, 300 participants (89.5 per cent) receiving tirzepatide had maintained at least 80 per cent of the weight lost during the lead-in, against 16.6 per cent of those receiving placebo ($p < 0.001$) (Figure 3) [1].

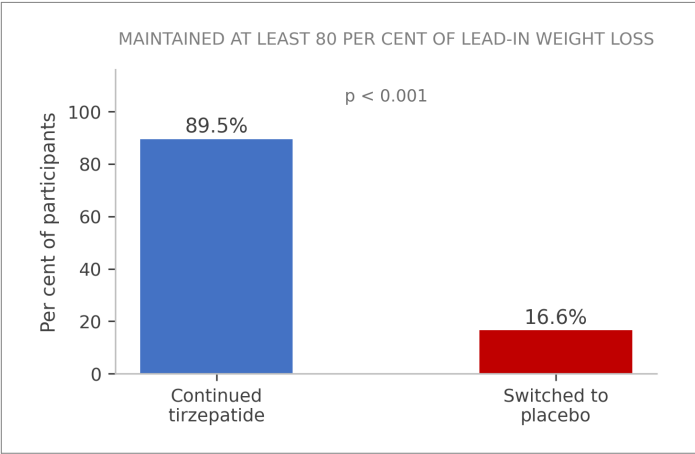


Figure 3: Participants maintaining at least 80 per cent of lead-in weight loss [1]

Where each group finished: Measured from study entry to week 88, mean weight reduction was 25.3 per cent in the tirzepatide group and 9.9 per cent in the placebo group (Figure 2) [1,9]. The placebo group therefore ended the trial substantially below its starting weight despite a year without active treatment.

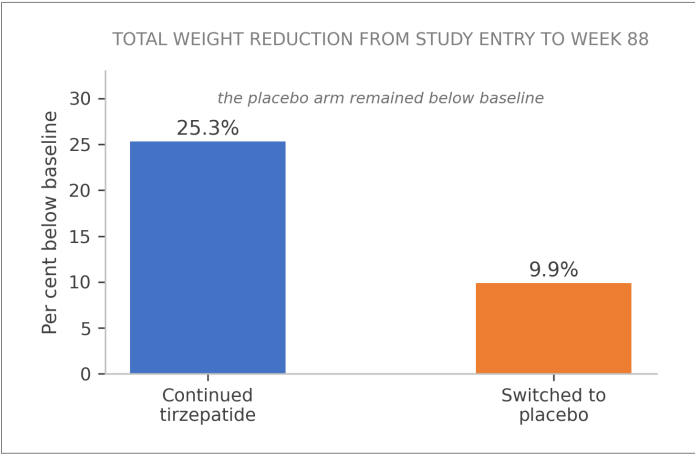


Figure 2: Total weight reduction from study entry to week 88 [1,9]

Outcome	Continued tirzepatide	Switched to placebo
Change, week 36 to 88	-5.5%	+14.0%
Difference	-19.4 points (95% CI -21.2 to -17.7)	p < 0.001
Maintained 80% of lead-in loss	89.5% (300 participants)	16.6%
Total change, week 0 to 88	-25.3%	-9.9%

Table 1: Principal outcomes of the randomised withdrawal trial, as reported by the original investigators [1]

How much was regained, and by whom: A post hoc analysis examined the 308 participants who had achieved at least 10 per cent weight reduction by week 36 and were then randomised to placebo. Mean age was 47.1 years and 71.1 per cent were women. Expressed as a proportion of the weight lost during the lead-in, 54 regained less than 25 per cent, 77 regained 25 to under 50 per cent, 103 regained 50 to under 75 per cent and 74 regained 75 per cent or more (Figure 4). Overall, 82.5 per cent regained at least a quarter of what they had lost (Figure 6) [10,11].

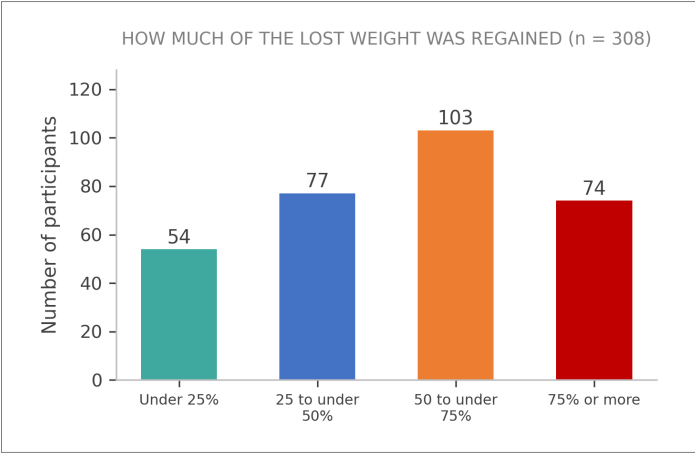


Figure 4: Distribution of weight regain among 308 withdrawn participants [10,11]

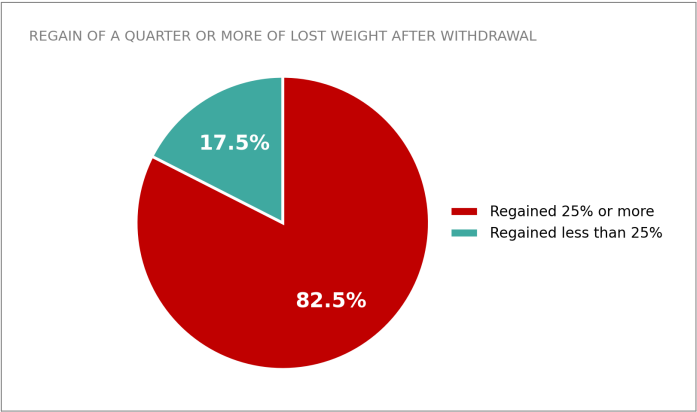


Figure 6: Proportion regaining a quarter or more of lost weight [10,11]

Cardiometabolic parameters: The same analysis assessed change in cardiometabolic measures between weeks 36 and 88 across those four regain categories, and reported that improvements achieved during the lead-in reversed to a degree that tracked the amount regained, with statistically significant differences across categories for systolic and diastolic blood pressure [10]. Health-related quality of life was assessed separately and favoured continued treatment [9].

Regain category	Participants	Share of the withdrawn group
Less than 25% of lost weight	54	17.5%
25% to under 50%	77	25.0%
50% to under 75%	103	33.4%
75% or more	74	24.0%

Table 2: Variation in regain after withdrawal among 308 participants [10,11]

Question	What the trial establishes
Does stopping cause regain?	Yes, on average 14.0% over 52 weeks
Does continuing hold the loss?	Yes, and adds a further 5.5%
Does everyone regain equally?	No; 54 of 308 regained under a quarter
Does withdrawal return people to baseline?	Not on average; placebo ended 9.9% below entry
Who should start treatment?	Not addressed by a withdrawal design

Table 3: What a randomised withdrawal design can and cannot answer [1,10]

What the class does beyond weight: The clinical case for continued treatment does not rest on weight alone. Randomised follow-up in this class has demonstrated reduction in cardiovascular events in people with obesity and no diabetes [26], and tirzepatide specifically has shown benefit in heart failure with preserved ejection fraction, in obstructive sleep apnoea and in the prevention of progression to type 2 diabetes [27,28,29]. If those benefits track exposure in the way weight does, withdrawal forfeits them too, though no trial has tested that directly.

How the comparators behave: The pattern is not specific to tirzepatide. Withdrawal of semaglutide in the extension of its

pivotal trial produced weight regain and reversal of cardiometabolic gains, and a separate randomised study of continued against discontinued treatment reached the same conclusion [4,5,18]. Head to head, tirzepatide produces greater weight reduction than semaglutide, but neither sustains its effect after stopping [19,33].

Discussion

The headline finding is unambiguous and clinically important. Withdrawing tirzepatide after a year of successful treatment produced a mean gain of 14.0 per cent over the following 52 weeks, while continuing produced a further loss of 5.5 per cent [1]. The editorial accompanying the post hoc analysis put the practical point plainly: there is a common assumption that these medicines can be stopped once a goal weight is reached, and this trial contradicts it [10].

Two qualifications are needed, and neither undermines the conclusion. The first is that withdrawal did not return participants to where they started. The placebo group finished 9.9 per cent below its baseline weight at week 88, having lost 20.9 per cent during the lead-in [1]. On average, then, roughly half the initial loss persisted a year after treatment stopped. That is a more moderate statement than the phrase weight regain usually conveys.

The second is variation. Among 308 withdrawn participants, 54 regained less than a quarter of what they had lost while 74 regained three quarters or more [10,11]. Those are very different outcomes from the same intervention, and the mean of 14 per cent describes neither group well. Nothing in the published analysis identifies in advance who will fall into which category, and that is the question a patient asking whether they can stop actually wants answered.

A structural point about the design deserves stating. A randomised withdrawal trial enrolls only those who tolerated and responded to the drug during an open-label lead-in, so its participants are an enriched population by construction [1,12]. That is appropriate for the question asked, which is what happens on stopping, and it means the trial says nothing about who should start, how many will tolerate treatment, or what proportion of an unselected population would reach a 20.9 per cent loss in the first place. Real-world cohorts suggest those proportions are considerably lower [13,14,31]. How a trial handles participants who stop is itself a methodological choice that changes the headline number [30].

The cardiometabolic findings tie the weight result to something that matters more. Blood pressure and glycaemic improvements reversed in proportion to the weight regained [10]. That supports treating obesity as a chronic condition requiring continued therapy, in the same way as hypertension, which is the conclusion the investigators themselves drew [1,15,18]. Benefit at the level of cardiovascular events has been demonstrated for this class in randomised follow-up [26,34], and

the degree of weight loss maps onto improvement in comorbidity [20,22]. It also raises a question this literature has not answered: whether intermittent, reduced-dose or supported-withdrawal strategies could preserve part of the benefit at lower cost and exposure. No trial reviewed here tested one.

There is also an economic dimension the trial does not address. If treatment must continue indefinitely to hold the benefit, then the relevant cost is not a course of therapy but an annual one for the rest of a patient life, and the decision to start carries a commitment that health systems have not generally budgeted for [15,32]. Persistence data from routine care show that most patients do not in fact continue for long, which means the population actually receiving this treatment resembles the withdrawal arm more closely than the continuation arm [13,14,31].

That observation gives the trial an unexpected practical reading. Its placebo arm is not merely a control condition; it is a reasonable model of what happens to the many patients who stop for reasons of cost, supply or tolerability. Interpreted that way, the 14 per cent regain is less a warning about deliberate discontinuation than a description of the common outcome, and the case for supporting persistence becomes the same case as the one for prescribing at all [13,31].

Study limitations

The limitations belong to the underlying literature. The trial is manufacturer-sponsored, as are the principal comparators in this field [1,8]. Participants were selected by successful completion of an open-label lead-in, so the population is enriched for tolerance and response and the results do not describe an unselected cohort [1,12]. The cohort was 80.1 per cent White and 71 per cent women, which limits generalisation [1]. Follow-up after withdrawal was 52 weeks, so the eventual trajectory is unknown and the trend at the point of censoring was still upward [1]. The regain distribution comes from a post hoc analysis restricted to those achieving at least 10 per cent loss, which is a further selection [10,11]. Cardiometabolic comparisons across regain categories were not randomised, since regain is an outcome rather than an allocation, so confounding is likely [10]. And no trial has compared abrupt withdrawal with dose reduction or intermittent continuation, which is the comparison a clinician facing cost or supply constraints actually needs [4,15].

Conclusion

Stopping tirzepatide after a successful year of treatment leads to substantial weight regain, averaging 14 per cent over the following year against a further 5.5 per cent loss in those who continued, and nine in ten of those continuing kept at least four fifths of what they had lost. The finding supports treating obesity as a condition requiring indefinite therapy rather than a course of treatment. Two things temper it: the withdrawn group still finished nearly 10 per cent below their starting weight, so regain was substantial rather than total, and it varied enormously between individuals, from under a quarter of the lost weight in 54 participants to three quarters or more in 74. Which patients fall where is not yet predictable, and that is the question the trial leaves open.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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