NEWSLETTER 24

Weight Regain After Stopping GLP-1s

Why obesity pharmacotherapy is long-term, disease-modifying treatment

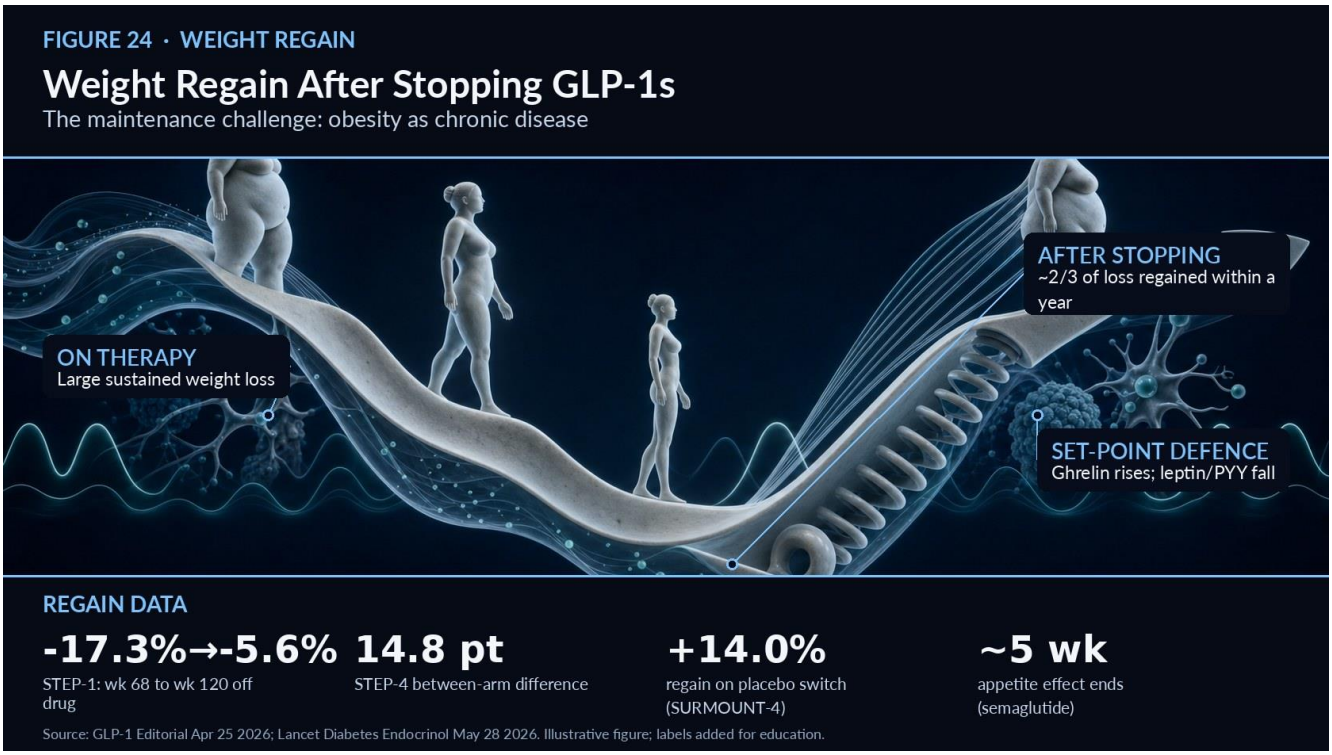

Figure 24. Weight Regain After Stopping GLP-1s — mechanism overview (illustrative; labels added for education).

One of the most clinically important lessons of the GLP-1 era is what happens when treatment stops. In the STEP-1 extension (327 participants), the semaglutide arm's weight change went from −17.3% at week 68 to −5.6% at week 120 after stopping—meaning patients regained about two-thirds of their prior weight loss within one year.[1] Discontinuation, in other words, largely undoes the gains.

Controlled comparisons make the effect unmistakable. In STEP-4, where 803 patients were randomised after a 20-week titration (mean −10.6%), continued semaglutide produced 7.9% additional loss while the placebo-switch arm regained 6.9%—a 14.8 percentage-point between-arm difference.[1] In SURMOUNT-4, after 36 weeks of open-label tirzepatide (mean −20.9%), continued tirzepatide lost a further 5.5% while the placebo-switch arm regained 14.0% over 52 weeks.[1]

The rebound is not merely cosmetic. Cardiometabolic gains—waist circumference, blood pressure, HbA1c, and lipids—reverted in parallel with weight regain after discontinuation, erasing much of the organ-level benefit that motivated treatment.[1]

The mechanisms explain the speed and consistency of relapse. Appetite suppression ends within roughly four to five half-lives (about five weeks for semaglutide), and adaptive thermogenesis, rising ghrelin, and falling leptin and PYY actively defend a lower set point—biology, not willpower, drives the regain.[1]

The consistency across three separate trials—STEP-1, STEP-4, and SURMOUNT-4—is what makes the finding so robust: whenever the drug was withdrawn, weight and cardiometabolic markers moved back toward baseline,

regardless of agent or starting point.[1] This argues strongly against using GLP-1 therapy as a time-limited "kickstart." Instead it should be planned, resourced, and consented to as ongoing treatment, with clinicians setting realistic expectations about duration and cost from the very first prescription.[2]

This maintenance challenge reframes how these drugs should be used. It underscores the 2026 guideline's framing of obesity pharmacotherapy as long-term, disease-modifying therapy rather than a short course—analogous to antihypertensives, which are not stopped once blood pressure normalises.[2] For clinicians and patients in India navigating cost and access, this evidence is essential for setting expectations: planning for sustained therapy, budgeting accordingly, and avoiding the disappointment and health reversal that follow abrupt discontinuation.[3]

References

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