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Early Weight Regain After GLP-1 Receptor Agonist Discontinuation: Mechanisms and Implications for Treatment De-Escalation Strategies

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed the pharmacological management of obesity, producing substantial and sustained weight loss during active treatment. However, discontinuation of therapy is frequently followed by significant weight regain, raising important questions regarding the durability of treatment effects and optimal strategies for treatment withdrawal. Recent systematic reviews and meta-analyses consistently demonstrate that weight regain after GLP-1RA discontinuation is substantial and follows a characteristic trajectory, with a large proportion occurring during the early post-cessation period. This front-loaded pattern suggests that the initial months after treatment cessation represent a critical window influencing long-term outcomes. Mechanistically, post-cessation weight regain appears to reflect the interaction of multiple processes. These include restoration of appetite following withdrawal of pharmacological GLP-1 signalling, compensatory increases in orexigenic hormones such as ghrelin, alterations in incretin balance including glucose-dependent insulinotropic polypeptide (GIP) and potential adaptive changes in GLP-1 receptor signalling pathways during prolonged pharmacological exposure, although evidence for a direct role in post-cessation weight regain remains limited. These converging mechanisms have important clinical implications, as abrupt discontinuation may result in a transient mismatch between increased biological drive for weight regain and the sudden loss of pharmacological appetite suppression. In this context, strategies aimed at mitigating early weight regain are of increasing interest. Recent randomised evidence suggests that reduced-intensity pharmacological maintenance may attenuate weight regain compared with abrupt discontinuation. However, whether structured tapering strategies can successfully facilitate treatment discontinuation remains unknown and requires prospective evaluation.

1 | Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related incretin-based therapies have reshaped the pharmacological management of obesity. Large randomised controlled trials have demonstrated mean weight reductions of approximately 15% with semaglutide and up to or exceeding 20% with tirzepatide, a dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist (GIP/GLP-1RA), representing an unprecedented degree of efficacy for anti-obesity pharmacotherapy [1, 2]. In addition to substantial weight loss, these agents improve cardiometabolic risk factors, including glycaemic control,

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blood pressure and lipid profiles, and have been associated with reductions in major cardiovascular events in selected populations [3, 4].

Despite this effectiveness, an important clinical question remains: what happens after treatment discontinuation? This issue is particularly relevant given the high discontinuation rates observed in routine clinical practice, with real-world evidence indicating that approximately half of individuals initiating GLP-1RA therapy discontinue within the first year, often due to cost, gastrointestinal adverse effects or limited access [5, 6]. Consequently, the long-term effectiveness of these therapies depends not only on their ability to induce weight loss but also on the durability of that weight loss after treatment cessation, for which both evidence and clinical guidance remain limited.

Recent systematic reviews have begun to address this evidence gap by synthesising data from randomised controlled trials and observational studies examining weight trajectories after discontinuation of GLP-1RAs and other weight management medications [7, 8]. These analyses consistently demonstrate substantial weight regain following cessation. However, important uncertainties remain regarding the magnitude, time course and underlying mechanisms of this regain and guidance on how best to discontinue these therapies or mitigate rebound weight gain remains limited in clinical practice.

This article is intended as a narrative review. Clinical and mechanistic literature was selected on the basis of relevance to post-GLP-1RA weight regain, treatment discontinuation and emerging treatment de-escalation strategies, with particular emphasis on recently published systematic reviews, randomised controlled trials and mechanistic studies. The review synthesises existing evidence relevant to weight regain following discontinuation of incretin-based therapies while critically discussing potential biological mechanisms and emerging approaches to long-term weight-loss maintenance.

Particular attention is given to the emerging observation that weight regain appears to be front-loaded in the early post-cessation period, suggesting that the initial months after discontinuation may represent a key window for intervention. On the basis of the currently available evidence, the review discusses individualised treatment de-escalation strategies, including response-guided tapering and lower-intensity maintenance approaches, as hypothesis-generating concepts warranting prospective evaluation for the mitigation of post-cessation weight regain.

2 | Recent Evidence on Weight Regain Following GLP-1RA Discontinuation

A recent systematic review and meta-analysis by Budini et al. examined weight regain following GLP-1RA cessation using a nonlinear meta-regression of post-treatment weight trajectories [8]. The review included 48 studies examining weight changes after discontinuation of GLP-1RAs in adults with overweight or obesity. However, only six randomised controlled trials were included in the final meta-regression model because these studies met predefined criteria for sample size, treatment efficacy and availability of longitudinal post-cessation data.

Using an exponential recovery model, the authors estimated that approximately 60% of the weight lost during treatment is regained within 1 year after discontinuation. Importantly, the model suggested that weight regain follows a decelerating trajectory, characterised by rapid early increases in body weight followed by progressively slower regain over time. Extrapolation of the model predicted that weight regain would plateau at approximately 75% of the weight lost during treatment, implying that some residual benefit may persist long term.

These findings provide an important quantitative framework for understanding post-cessation weight dynamics. The nonlinear model aligns with physiological expectations, as rapid early changes in energy balance are likely to be followed by stabilisation as body weight approaches a new equilibrium.

However, the interpretation of the plateau estimate requires caution. The vast majority of the trials included in the meta-regression reported follow-up periods of 52 weeks or less after cessation, meaning that predictions beyond this time horizon are based on statistical extrapolation rather than direct observation. In addition, the trials included in the analysis varied in several important respects, including treatment duration, patient populations and the presence or absence of behavioural support during follow-up. Because post-cessation outcomes were rarely the primary endpoint of these trials, weight data after discontinuation were often limited to one or two time points. As a result, although the meta-regression provides valuable insights into the general trajectory of weight regain, it may not fully capture the heterogeneity of responses across different clinical contexts. Nevertheless, one consistent feature emerges across studies: a substantial proportion of weight regain occurs within the first months after treatment discontinuation, suggesting that the early post-cessation period plays a critical role in determining long-term outcomes [8].

A second systematic review by West et al. examined weight regain following cessation of a broader range of weight management medications, including both incretin-based therapies and older pharmacological agents [7]. This analysis included 37 studies comprising more than 9000 participants and used several complementary modelling approaches to estimate rates of weight regain after treatment discontinuation.

Across all weight management medications, the authors estimated an average weight regain of approximately 0.4 kg per month after cessation of therapy, or 0.3 kg per month relative to control in randomised trials. On the basis of this rate, body weight was projected to return to baseline within approximately 1.7 years after discontinuation. When analysis was restricted to incretin-based therapies, monthly weight regain was higher, reflecting the larger initial weight loss achieved with these agents, averaging 0.5 kg per month (95% CI: 0.4–0.7) for incretin mimetics overall and 0.8 kg per month (95% CI: 0.7–0.9) for newer, more effective incretin mimetics. The review also examined changes in cardiometabolic markers after treatment cessation.

Improvements in HbA1c, fasting glucose, blood pressure and lipid levels observed during active treatment were found to diminish over time, with projections suggesting return towards baseline within approximately 1.4 years after discontinuation. An additional finding of this analysis was that weight regain after cessation of pharmacotherapy appears to occur more rapidly than after behavioural weight management programmes. Although pharmacological treatments produced greater initial weight loss, the estimated rate of regain following cessation was significantly faster than that observed after structured lifestyle interventions [7].

While these findings reinforce the conclusion that weight regain after pharmacotherapy cessation is substantial, several methodological considerations complicate their interpretation. The review included medications spanning several decades of obesity pharmacotherapy, many of which differ markedly from contemporary incretin-based therapies in both mechanism of action and magnitude of weight loss. Consequently, the overall estimates of regain may not fully reflect the dynamics specific to GLP-1RAs and related agents. Moreover, follow-up periods in the vast majority of the included studies were relatively short, typically ranging from 6 to 104 weeks. In particular, data on the newest and most effective incretin therapies remain limited, meaning that projections of long-term outcomes rely heavily on extrapolation.

3 | Interpreting the Trajectory of Weight Regain

Despite methodological differences, the two systematic reviews converge on several key conclusions. First, weight regain following discontinuation of GLP-1RA therapy is substantial. Whether expressed as a proportion of weight lost or as an absolute rate of regain, the available evidence consistently indicates that a large share of treatment-induced weight loss is reversed after cessation. Second, the time course of regain appears to be front-loaded, with relatively rapid increases in body weight during the initial months after discontinuation. Although the precise trajectory varies across studies, the early post-cessation period consistently emerges as the phase during which the largest changes occur. Third, long-term outcomes remain uncertain. Some modelling approaches suggest that weight regain may plateau below baseline levels, whereas others project a return to baseline body weight within approximately 1.5–1.7 years after treatment cessation. These differences largely reflect methodological assumptions about the shape of the weight–regain curve rather than direct long-term empirical observations. Finally, there is substantial individual variability. Even within controlled clinical trials, some participants maintain a portion of their weight loss after discontinuation, whereas others experience rapid rebound [7, 8].

A parsimonious explanation for the characteristic front-loaded curve pattern of weight regain is that pharmacological appetite suppression is removed at a time when body weight remains furthest from its previously defended equilibrium. This may result in a rapid early increase in energy intake, followed by progressive slowing of weight regain as body weight and appetite regulation gradually move towards a new equilibrium.

4 | Mechanistic Insights Into Post-Cessation Weight Regain

The mechanisms underlying post-cessation weight regain are likely multifactorial, involving complex interactions between physiological and hormonal processes, with behavioural factors acting as potential modifiers. A conceptual overview of these interacting pathways, including the proposed mismatch between biological drive and endogenous appetite regulation following treatment cessation, is presented in Figure 1, which integrates these mechanisms into a unified framework.

4.1 | Restoration of Appetite and Satiety Signalling

GLP-1RAs promote weight loss primarily by suppressing appetite and enhancing satiety through central nervous system pathways, including activation of hypothalamic melanocortin pathways (POMC/CART) and inhibition of NPY/AgRP neurons, as well as modulation of brainstem nuclei and mesolimbic reward circuits [9].

These effects reduce caloric intake and facilitate sustained negative energy balance during treatment. When therapy is discontinued, this pharmacological modulation of appetite disappears, allowing pre-existing patterns of energy intake to re-emerge [9, 10].

4.2 | Changes in Gut Hormone Signalling: Ghrelin and GIP

In addition to general homeostatic responses to weight loss, alterations in gut-derived hormones may contribute to post-cessation weight regain. In particular, ghrelin and GIP have been proposed as modulators of appetite and energy balance following discontinuation of incretin-based therapies [9].

Ghrelin, an orexigenic hormone primarily produced in the stomach, plays a central role in the regulation of hunger and food intake. Circulating ghrelin levels are known to increase following weight loss, representing a well-established compensatory response aimed at restoring energy balance. A longitudinal study of diet-induced weight loss has demonstrated that these elevations may persist for at least 1 year and are associated with increased appetite and weight regain [11]. Although longitudinal data during and after GLP-1RA therapy remain limited, the weight loss induced by these agents is likely to engage overlapping compensatory mechanisms. Notably, GLP-1RAs suppress appetite primarily through central pathways, including hypothalamic and mesolimbic circuits, while effects on circulating ghrelin levels appear inconsistent across studies in both humans and animal models [12–14]. As a result, compensatory orexigenic signalling associated with weight loss may not be fully suppressed during treatment and may persist following cessation. Upon discontinuation, the loss of pharmacological appetite suppression may therefore unmask this persistent biological drive, contributing to a rapid increase in hunger and energy intake during the early post-cessation period.

GIP may also contribute to post-cessation metabolic adaptation. Beyond its incretin effect on insulin secretion, GIP has been implicated in adipose tissue metabolism and energy storage.

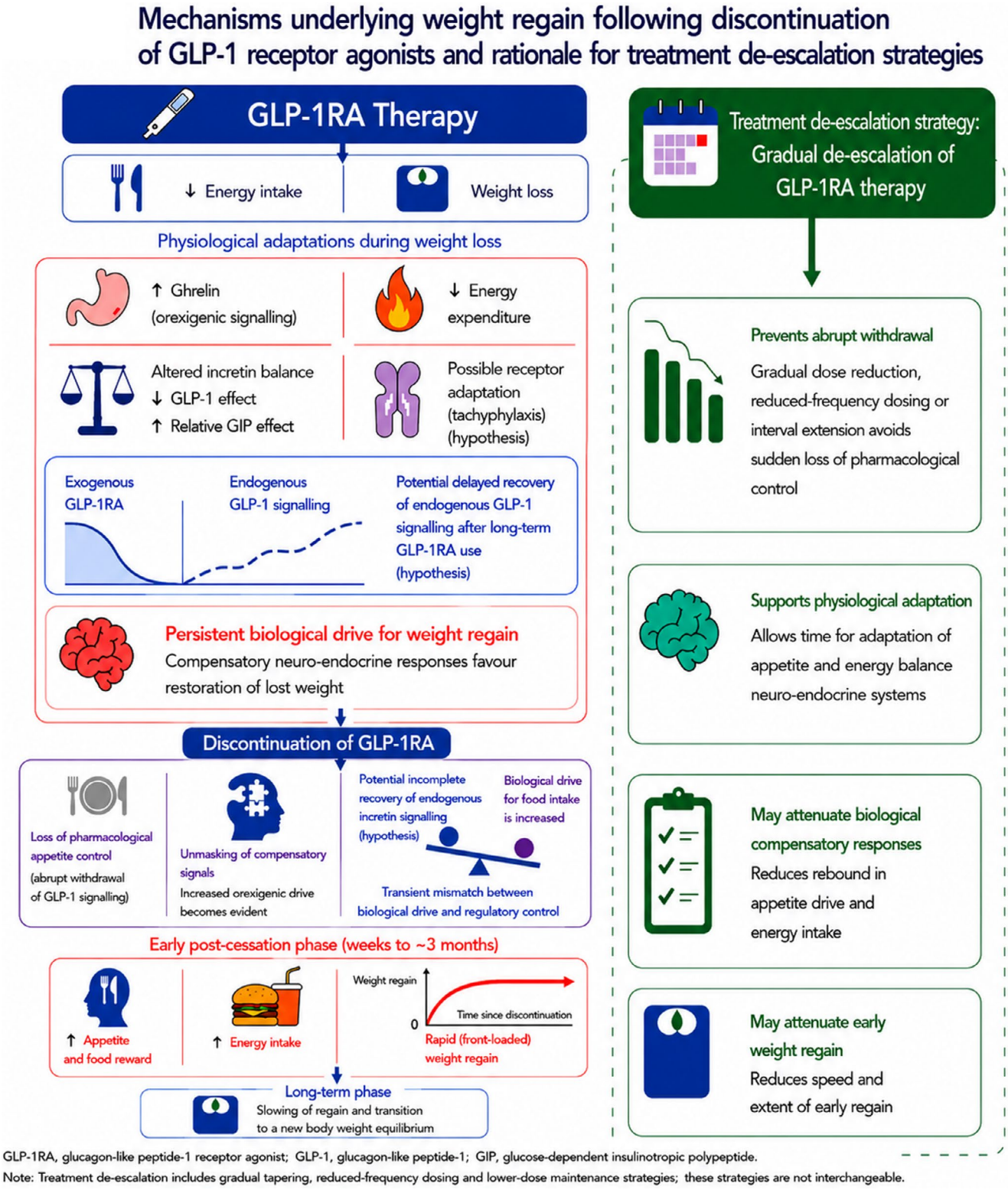

FIGURE 1 | Following discontinuation of GLP-1 receptor agonists (GLP-1RAs), the loss of pharmacological appetite suppression coincides with persistent compensatory responses to weight loss, including increased orexigenic signalling and reduced energy expenditure. Together, these processes may contribute to a transient mismatch between the biological drive for weight regain and endogenous appetite regulation, promoting rapid early weight regain followed by gradual re-equilibration. Additional mechanisms, including altered incretin balance and potential receptor-level adaptations, remain hypothetical and are presented as possible modifiers rather than established drivers of post-cessation weight regain. Treatment de-escalation strategies, including lower-dose maintenance, reduced-frequency dosing and gradual tapering, may attenuate early weight regain by avoiding abrupt withdrawal of pharmacological support and allowing more progressive physiological adaptation.

Experimental and clinical data suggest that GIP signalling can promote lipid deposition and has been associated with energy storage and adiposity [15, 16]. During treatment with dual GIP/GLP-1RAs, pharmacological modulation of incretin pathways may alter energy partitioning and appetite regulation. Following discontinuation, the abrupt withdrawal of GLP-1-mediated appetite suppression, in combination with persistent compensatory responses to weight loss, may result in a relative shift in incretin balance favouring energy storage and increased energy intake. Although direct evidence for this mechanism remains limited, it is consistent with the established physiological roles of GIP and broader adaptive responses to weight reduction [15, 16]. However, the role of GIP signalling in obesity remains complex and incompletely understood. Both GIP receptor agonism and GIP receptor antagonism have been associated with weight reduction in experimental and clinical settings, highlighting the complex and incompletely understood role of GIP signalling in obesity pharmacotherapy [2, 15]. Consequently, any contribution of post-cessation alterations in GIP signalling remains hypothetical, and current evidence is insufficient to establish its role in post-cessation weight regain, particularly when extrapolating findings from dual GIP/GLP-1RAs to GLP-1RAs as a class.

Importantly, the available data do not allow firm causal inferences regarding the role of ghrelin or GIP in post-cessation weight dynamics [11, 15]. Most studies have focused on diet-induced weight loss or on the effects of incretin-based therapies during active treatment rather than after discontinuation. In interpreting these mechanisms, it is important to distinguish evidence specific to GLP-1RA discontinuation from physiological responses known to occur after weight loss more generally. The front-loaded pattern of weight regain is supported by discontinuation trials and post-cessation meta-analyses, whereas several proposed hormonal and receptor-level mechanisms are extrapolated from broader weight-loss physiology or from studies conducted during active incretin-based treatment.

Nevertheless, the convergence of these physiological responses provides a coherent and biologically plausible framework for understanding the rapid early phase of weight regain observed in clinical studies. These mechanisms are likely to act in concert rather than in isolation, reinforcing the overall biological drive towards weight regain.

4.3 | Potential Adaptation of Incretin Signalling Pathways

A potential explanation for rapid post-cessation weight regain relates to adaptive changes in GLP-1 receptor signalling during prolonged pharmacological stimulation. Experimental studies have shown that certain GLP-1–mediated physiological responses, most notably slowing of gastric emptying, attenuate with repeated exposure to GLP-1 agonists. However, this evidence largely concerns gastrointestinal motility rather than long-term regulation of appetite or body weight, whereas direct evidence for receptor-level adaptations in central appetite-regulating pathways following treatment discontinuation remains lacking [17–19].

The most parsimonious explanation for early regain remains the abrupt removal of pharmacological appetite suppression in the setting of persistent biological adaptations to prior weight loss. Whether receptor-level adaptations independently contribute to this transition remains unknown and warrants mechanistic investigation.

More broadly, the early post-cessation period may be characterised by a transient mismatch between biological drive and endogenous regulatory control, potentially representing a modifiable target for future intervention strategies.

5 | De-Escalation Strategies

Lower-dose maintenance and tapering-to-discontinuation should be viewed as related but fundamentally distinct de-escalation strategies. Lower-dose maintenance aims to identify a reduced but ongoing pharmacological intensity that is sufficient to preserve most of the achieved weight loss, thereby accepting continued treatment as part of long-term obesity management. In contrast, tapering-to-discontinuation aims to progressively reduce treatment exposure with the goal of complete cessation while minimising early rebound in appetite, food preoccupation and body weight. These strategies, therefore, differ in their intended endpoint, clinical assumptions and criteria for success.

Recently, the SURMOUNT-MAINTAIN trial provided randomised controlled evidence that reducing treatment intensity can attenuate weight regain compared with abrupt discontinuation [20]. In this Phase 3b trial, adults with obesity who had achieved weight reduction after 60 weeks of open-label tirzepatide at the maximum tolerated dose were randomised to continue maximum tolerated dosing, reduce tirzepatide to 5 mg or switch to placebo for 52 weeks. Continued maximum tolerated dosing almost completely maintained prior weight loss, with 96.5% of the initial bodyweight reduction preserved among participants who had reached a weight plateau. Dose reduction to 5 mg preserved a substantial but smaller proportion of weight loss, with 67.9% of the initial reduction maintained, compared with 42.8% after switching to placebo. Similarly, 42.4% of participants in the 5 mg group maintained at least 80% of their prior weight loss, compared with 10.4% in the placebo group and 77.5% in the continued maximum tolerated dose group. Rescue tirzepatide for the regain of at least 50% of lost bodyweight was required in 24.6% of participants assigned to 5 mg, compared with 67.9% assigned to placebo and 7.9% continuing maximum tolerated dosing. These findings suggest that lower-dose maintenance can provide partial protection against weight regain and may be sufficient for some individuals, but responses are heterogeneous and full-dose continuation remains more effective.

However, SURMOUNT-MAINTAIN evaluated fixed maintenance dose reduction rather than progressive tapering towards treatment discontinuation and therefore does not directly address whether gradual withdrawal can prevent rebound weight regain [20]. Lower-dose maintenance and tapering-to-discontinuation should therefore be viewed as related but distinct de-escalation strategies, supported by different levels of evidence.

Given the rapid and often front-loaded pattern of weight regain after GLP-1RA discontinuation, strategies that avoid abrupt withdrawal of pharmacological appetite suppression are of increasing clinical interest. Conceptually, gradual de-escalation may allow appetite, satiety and energy-balance systems to recalibrate more progressively while also potentially allowing time for behavioural adaptation and reinforcement of weight-maintenance strategies. Until recently, evidence supporting such de-escalation strategies was largely limited to retrospective or uncontrolled real-world studies.

Wong et al. reported a case series in which selected patients transitioned from weekly semaglutide or tirzepatide to reduced-frequency dosing and maintained weight loss, body composition and metabolic improvements over a mean follow-up of 36 weeks [21]. Similarly, Seier et al. described a real-world, symptom-guided treat-to-target tapering approach, in which GLP-1RA doses were gradually reduced while maintaining dosing frequency, with dose adjustments guided by weight fluctuations, satiety and hunger perception and upward titration permitted when clinically needed. At Week 64, mean weight loss remained 16.7% (95% CI: 16.0–17.4) [22].

Although these studies provide preliminary support for de-escalation strategies, their interpretation is limited by retrospective or uncontrolled designs, potential selection bias, heterogeneous tapering approaches and the absence of randomised comparisons. Consequently, fixed lower-dose maintenance currently has the strongest evidentiary support among de-escalation strategies, whereas reduced-frequency dosing and tapering-to-discontinuation should be regarded as promising but still investigational approaches requiring prospective evaluation.

6 | Discussion and Conclusion

The rapid weight regain observed after discontinuation of GLP-1RA therapy highlights the early post-cessation period as a potential target for preventive intervention.

In current clinical practice, discontinuation is often approached as a binary decision: patients either continue therapy indefinitely or stop abruptly [5, 6]. However, this approach may not adequately account for the physiological adjustments that occur when pharmacological appetite suppression is withdrawn. As discussed, weight loss is accompanied by compensatory increases in orexigenic signalling, including elevated ghrelin levels, while the removal of GLP-1-mediated appetite suppression may unmask these signals. In addition, alterations in incretin balance, including potential shifts in GIP signalling, may further contribute to increased energy intake and storage in the post-cessation phase.

The role of lifestyle intervention in addressing post-cessation weight regain remains uncertain. Although discontinuation of structured lifestyle support is a recognised contributor to weight regain [23], the systematic reviews by Budini and West included heterogeneous studies in which lifestyle intervention was variably implemented, continued or withdrawn [7, 8]. However, for incretin-based therapies, the available randomised evidence suggests that early post-discontinuation weight regain cannot be fully explained by withdrawal of lifestyle support. In all three randomised controlled trials evaluating GLP-1RA discontinuation, lifestyle intervention was continued in both study arms, yet participants randomised to placebo consistently demonstrated a rapid and front-loaded pattern of weight regain [20, 24, 25]. These findings suggest that withdrawal of GLP-1RA therapy itself, rather than cessation of lifestyle support alone, may be an important determinant of early post-treatment weight regain. In general, behavioural adaptation, dietary quality, physical activity, resistance training and long-term adherence are likely to contribute to interindividual variability in post-cessation outcomes and should therefore be incorporated into future maintenance, discontinuation and de-escalation studies.

As illustrated in Figure 1, gradual treatment de-escalation may allow more progressive recalibration of appetite and energy-balance systems while providing time to reinforce behavioural weight-maintenance strategies.

Evidence from dose-de-escalation studies supports the broader concept that GLP-1RA discontinuation should not necessarily be viewed as a binary choice between indefinite full-dose therapy and abrupt cessation. In addition, the recently published ATTAIN-MAINTAIN trial suggests that ongoing pharmacological support through transition to oral incretin-based therapy may attenuate post-treatment weight regain, although this strategy represents treatment maintenance rather than treatment de-escalation or tapering [25].

Response-guided dose or dosing interval reduction may represent clinically relevant approaches deserving further investigation. However, the available evidence remains limited and does not yet establish whether structured dose-de-escalation can effectively prevent early rebound weight regain.

Taken together, the current evidence hierarchy supports continued treatment and fixed lower-dose maintenance as the most evidence-based approaches for preserving weight loss after incretin therapy.

Future research should directly compare lower-dose maintenance and treatment de-escalation strategies while incorporating patient-centred measures such as appetite control and food noise to identify the lowest effective level of pharmacological support required for sustained weight-loss maintenance. Whether some individuals can ultimately maintain weight loss after progressive treatment de-escalation and eventual cessation of therapy remains unknown. Response-guided approaches incorporating weight stability, appetite control, food noise and early weight-regain signals may help identify which patients require ongoing pharmacological support and which may successfully transition off treatment.

In addition, post-cessation outcomes should be evaluated separately across different incretin-based therapies, as weight-regain trajectories may differ between GLP-1RAs and dual GIP/GLP-1RAs. Nevertheless, the consistent observation of a front-loaded pattern of weight regain following treatment withdrawal provides a strong rationale for prospective evaluation of de-escalation strategies after incretin-induced weight loss.

Author Contributions

M.A.D. and F.H.v.B. contributed equally to the conception, drafting and critical revision of the manuscript. E.N.v.R. contributed to the critical revision of the manuscript. All authors approved the final version and agree to be accountable for all aspects of the work.

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