REBOUND OBESITY AFTER GLP–1 AGONISTS DISCONTINUATION

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ABSTRACT

Introduction: Discontinuation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) often results in rebound obesity and excessive weight regain. This review explores the physiological, psychological, and behavioural factors contributing to weight regain after the discontinuation of GLP-1 RAs**. Methods:** This narrative review involved a review of literature published in PubMed, Scopus, Embase, Web of Science, and Google Scholar. The search for peer-reviewed literature in English started on 8 March 2025 and was repeated for updates on 25 March 2025. **Results:** The literature search identified only five studies that examined weight regain following the discontinuation of GLP-1 RAs. These studies found that some users of these agents had regained the weight they lost before upon discontinuing GLP-1 RAs. The proposed mechanism for this phenomenon is that abrupt cessation of appetite inhibition induced by GLP-1RAs leads to a surge in hunger, reduced energy expenditure, and fat mass gain. Psychological factors, like emotional overeating and dependence on the therapy, further exacerbate rebound**. Conclusion:** This review focuses on the complex phenomenon of rebound obesity that may develop upon GLP-1 RAs discontinuation, emphasizing the need for comprehensive strategies to manage weight regain. Potential approaches include gradual dose reduction, combination therapies, and lifestyle interventions to mitigate weight regain.

Keywords: GLP-1 receptor agonists, weight gain, discontinuation

INTRODUCTION

Obesity is a chronic state associated with various health complications such as cardiovascular diseases, type 2 diabetes, and deterioration of life quality (Christensen, 2020). Thus, obesity is not merely an aesthetic problem but a chronic health condition that needs long-term management (Perdomo et al., 2023). The rising prevalence of obesity is evident all over the world. In the United States alone, around 73% of adults are either overweight or obese. Nearly 650 million worldwide are considered obese (Deng et al., 2024; Kocatepe et al., 2025). This increasing epidemic stands to have huge public health implications as it causes chronic diseases and imposes nearly $173 billion in medical costs every year (Ward et al., 2021).

In this regard, pharmacological interventions are considered critical in managing obesity. Among these, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including liraglutide, semaglutide, and tirzepatide, have made major innovations in the treatment of obesity, achieving clinically significant weight loss based on trial evidence (Davies et al., 2015; Amaro et al., 2022; Aronne et al., 2024; Son & Lim, 2024). These agents increase satiety signals in the brain, delay gastric emptying, and improve glycaemic control, addressing both obesity's physiological and metabolic aspects (Drucker, 2022). For instance, semaglutide is associated with an estimated 15–20% weight loss from baseline weight after consistent use over 68 weeks (Wilding et al., 2022). Likewise, liraglutide demonstrated prolonged weight loss after two years, leading study participants to lose a mean of 8% of their baseline weight (Wadden et al., 2013).

As useful as they are, GLP-1 RAs are not a cure for obesity but tools for part and parcel of a patient's lifelong commitment to weight management. Increasingly, clinicians are becoming concerned about the rapid and excessive weight regain that follows such medications' discontinuation (Perdomo et al., 2023; Wilding et al., 2022). *This review focuses on the complex phenomenon of rebound obesity following the discontinuation of GLP-1 receptor agonists*. In combining much of the available knowledge and carefully considering physiological, psychological, and behavioural features, this article will help clarify the mechanisms by which rebound obesity occurs and how it might be anticipated. Understanding these intricacies will also ensure optimal treatment protocols and maintenance of results in weight management of patients on GLP-1 RAs.

The considerations of rebound obesity are certainly physiological, yet there are also psychological and behavioural considerations to consider (Montecinos et al., 2024). Many patients think they have lost weight due to treatment and not by their efforts, so they feel unprepared for self-management when the treatment stops (Perdomo et al., 2023). The follow-up continuous weight management is also disrupted by socioeconomic barriers such as cost and access (Rodriguez et al., 2025). The high treatment cost among low-income communities increases the risk of discontinuation and, subsequently, rebound obesity (Talay & Vickers, 2024). The present review aims to highlight these issues and describe their interrelationship with mechanisms underlying rebound obesity, as well as suggest possible means to manage it.

METHODS

The search methodology for this narrative review was comprehensive and aimed to capture current relevant evidence on GLP-1 RAs medication use for weight loss and discontinuation. To gather information and prepare this narrative review, PubMed, Scopus, Embase, Web of Science, and Google Scholar were searched for peer-reviewed literature in English on 8 and 9 March 2025 and again for updates on 25 March 2025. Clinical trial protocols from ClinicalTrials.gov were also scrutinized. Key terms included "obesity," "GLP-1 receptor agonists," "weight regain," "weight loss," "liraglutide," "semaglutide," and "tirzepatide."

Data extraction focused on studies reporting weight regain after GLP-1 RA discontinuation, mechanisms driving rebound obesity, and strategies to mitigate weight regain. The inclusion criteria encompassed randomized controlled trials published within the last decade. The literature search identified only five studies that examined weight regain following the discontinuation of GLP-1 RA. Studies were evaluated for their methodological rigor, sample size, and relevance to the research question. Supplementary data, such as patient-reported outcomes and real-world evidence, were also considered to provide a broader perspective on the challenges of discontinuing GLP-1 RAs.

RESULTS

In this narrative review, five randomized clinical trials were summarized. These studies vary in sample size, duration, and reported outcomes, providing a useful overview of the rebound effect across different agents. Adult individuals with an elevated Body Mass Index from both sexes were included in these studies. Individuals with comorbidity or with diabetes mellitus were excluded. Intervention was the administration of GLP-1 RAs for some time, then randomizing participants into two groups. One group continued on GLP-1 RAs while the other group received a placebo. All studies reported an increase in weight after discontinuation of these medications.

Table 1 summarizes key clinical studies investigating the extent of weight regain after discontinuing various GLP-1 RAs.

Author(s)	GLP-1 RA	Study Type	N	Duration	Weight Regain After Discontinuation	Reported Side Effects	Dosage
Wadden et al. (2013)	Liraglutide	Randomized Trial	300	56 weeks	1.9% weight regain after 1 year	None reported	Daily injection, 3 mg
Rubino et al. (2021)	Semaglutide	Randomized Trial	902	68 weeks	6.9% weight regain after stopping semaglutide	Gastrointestinal adverse effects	Weekly injection, 2.4 mg
Wilding et al. (2022)	Semaglutide	Randomized Trial	450	68 weeks	11.6% weight regain after stopping semaglutide	Worsening cardiometabolic markers	Weekly injection, 2.4 mg
Lopez-Jimenez et al. (2022)	Tirzepatide	Randomized Trial	400	36 weeks	14% weight regain post-discontinuation	Muscle weakness	Weekly injection, 5 mg
Aronne et al. (2024)	Tirzepatide	Randomized Trial	783	36 weeks	14% weight regain post-discontinuation	Muscle weakness	Weekly injection, 5 mg

DISCUSSION

This review explores the physiological, psychological, and behavioural factors contributing to weight regain after the discontinuation of GLP-1 RAs. The five studies reported a small percentage of weight gain after discontinuing treatment with GLP-1 RAs. Following the discontinuation of GLP-1 RAs, rebound obesity becomes a substantial management problem. Their efficacy in being weight reducers has also ended as sudden cessation leaves most patients regaining the lost weight. Hence, effective means and measures need to be derived to mitigate these adverse effects as well as sustain weight loss after therapy withdrawal. Probably the most effective method to avoid rebound obesity might well be the tapering of GLP-1 RAs. Sudden stoppage of these medicines has been associated with a massive increase in food craving and appetite, once the appetite-suppressing effects of GLP-1 RAs are removed. When medicines are reduced over a relatively long period, the patient gradually learned to live without the misery of their effects, subsiding hunger, and satiation This approach is deemed to alleviate

common side effects such as nausea and vomiting (Filippatos et al., 2015); however, no prototype tapering schedule is yet established. More studies to define optimal tapering schedules that minimize rebound effects and ensure patient safety need to be done.

Combining GLP-1 RAs with other pharmacological agents may help sustain weight loss and prevent rebound obesity. For example, metformin has shown sufficient efficacy in improving insulin sensitivity and has been clinically effective in combination with GLP-1 RAs for weight management (Jensterle et al., 2024). Insulin resistance, often seen in obese patients, may be an excellent adjunct for weight loss caused by GLP-1 RAs. Medications such as sodium-glucose co-transporter two inhibitors, which operate by mechanisms different from those of GLP-1 RAs, may benefit the prevention of weight regain after discontinuation. Such a combination treatment requires further evaluation in clinical trials for effectiveness and safety in long-term weight maintenance.

Behavioural and lifestyle interventions are equally important. Behavioural and lifestyle interventions require equally important pharmacological treatments for the long-term management of obesity. Structured lifestyle programs that include diet modification, regular physical activity maintenance, and behavioural-change techniques have been shown to be effective in preventing rebound obesity after stopping therapy with the GLP-1 RAs (Dash, 2024). Their help is extended in maintaining and addressing behavioural processes that contribute to weight gain.

Exercise is critical to suppress the metabolic adaptations following the cessation of GLP-1 RA therapy. Typically, upon stopping GLP-1 RAs, there is a more pronounced gain in fat mass than lean body mass, worsening the metabolic risks of insulin resistance and dyslipidemia (Jensen et al., 2024). Physical activity is essential for sustaining lean body mass and basal metabolic rate, which could be affected after discontinuing GLP-1 RA therapy (Papathanasiou et al., 2020). Thus, integrating a structured exercise program into the weight management plan is vital for halting further fat accumulation and helping maintain weight in the long term. Some challenges arise due to the patients' adherence to these exercise regimens. Thus, a more individualized approach must be considered, including personal preferences, barriers to participation, and overall health status.

Psychological factors significantly contribute to the occurrence of rebound obesity. Many patients consider weight loss a result of medication rather than their effort, creating an inability to take ownership of this weight-loss success and, therefore, feel dependent upon the drug during that time. Inability to manage weight without pharmacotherapy after discontinuation creates barriers for many patients towards intrinsic motivation for any future behavioural changes to maintain the weight (Perdomo et al., 2023).

The transitional time calls for psychological support, cognitive-behavioural therapy, and motivational interviewing. These interventions can be extended to patients to rehabilitate their self-worth in managing weight alone, since they equip a patient with the much-needed tools to make long-lasting behavioural changes (Barrett et al., 2018). Psychological interventions lessen the emotional and cognitive hurdles that predispose to weight regain, including emotional eating and a sense of

failure in instances of cessation (Chawner & Filippetti, 2024).

The other factor affecting the discontinuation of GLP-1 RAs and weight regain is economic challenges related to the costs of medicines. Cost-related barriers have been reported to disadvantage lower-income patients in adhering to their treatments, ultimately exposing them to rebound obesity risk (Rodriguez et al., 2025). Improving access to cheaper pharmaceuticals and other alternative treatment forms is necessary and important in decreasing the economic burden of weight control.

In addition, digital health solutions like telemedicine, mobile applications, and remote monitoring applications can provide continuous patient support for maintaining weight loss even during limited access to personal health care (Talay & Alvi, 2024). They also help keep the continuity of care and give ward-based guidance and motivation to patients following discontinuation.

Even if there are approaches, several unsolved questions remain regarding rebound obesity after discontinuation of the GLP-1 RAs. The long-term metabolic effects of discontinuation, especially in younger individuals or in patients suffering from multiple comorbidities, remain unspecified. Further research is warranted to evaluate how long-term GLP-1 RA use and its cessation affect other secular components of health.

Further study into the best ways to discontinue GLP-1 RA therapy that lacks standard tapering protocols highlights the need for more research in this area. The most effective tapering protocols can help guide patients through their tapering process and make rebound weight gain less likely. Future research should also investigate the newer generation of GLP-1 RAs that can provide more sustainable options for weight control with fewer adverse effects. These new agents would possibly combine GLP-1 RAs with other weight-loss mechanisms to yield more comprehensive treatments for obesity.

CONCLUSION

GLP-1 RAs have greatly improved the treatment of obesity; however, upon discontinuation, weight gain may rebound with other metabolic risk factors. Hence, it becomes imperative to strategize holistically, involving gradual tapering, cognitive behavioural therapy, motivational interviewing, and lifestyle changes. Future studies should also focus on developing standardized tapering protocols, next-generation GLP-1 RAs, and more effective ways of long-term weight maintenance. Filling these gaps will help to improve the sustainability of weight loss achieved and lessen the burden of health issues related to obesity.

Conflicts of Interest

The authors declare no conflicts of interest.

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