

Review

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Posted Date: 9 October 2026

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Review

Glucagon-Like Peptide-1 Receptor Agonists in Obesity: Evidence for Dose Reduction and Durable Weight Loss Maintenance

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Abstract

Obesity is a chronic disease that is a major risk factor for serious, long-term health complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of pharmacotherapies that are highly effective in the treatment of obesity, producing weight loss of 15-20% or greater in clinical trials. Current clinical guidance recommends continued therapy to sustain these benefits; however, barriers including cost, limited access, and adverse effects may inhibit long-term use and contribute to high discontinuation rates. Abrupt discontinuation of GLP-1RA therapy is problematic as it is associated with significant weight regain and reversal of cardiometabolic improvements. Given the challenges associated with prolonged treatment, there is a critical need to develop evidence-based strategies that support patients who reduce or discontinue GLP-1RA therapy. This paper explores the scientific premise for structured dose-reduction approaches, coupled with behavioral and psychological interventions, to promote durable weight-loss maintenance following GLP-1RA therapy.

Keywords: glucagon-like peptide-1 receptor agonist; obesity; weight loss maintenance

1. Introduction

Obesity is a chronic, multifactorial disease affecting 41.9% of US adults and is associated with increased risk of comorbidities and overall mortality [1]. Effective management involves long-term interventions, including lifestyle changes, bariatric surgery, and pharmacotherapy [2]. Historically, bariatric surgery has been the most effective intervention, yielding 25-35% total weight loss [3]. However, the novel pharmaceutical class of glucagon-like peptide-1 receptor agonists (GLP-1RA) are approaching similar levels of efficacy, making them an increasingly desirable treatment for obesity management.

GLP-1RA use has grown rapidly, with approximately one in eight US adults reporting having used a GLP-1RA medication [4]. Several GLP-1RA's are approved for weight management, including liraglutide, semaglutide, and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide. These medications promote weight loss through central and peripheral mechanisms that decrease appetite, increase satiety, delay gastric emptying, and improve glucose homeostasis [5]. Tirzepatide additionally activates GIP receptors, which further enhances weight loss and cardiometabolic outcomes through complementary metabolic effects [6]. Clinical trials have demonstrated significant weight reductions of approximately 6.4% [7], 14.9% [8], and 20.9% [9], with liraglutide, semaglutide, and tirzepatide, respectively, alongside significant improvements in cardiometabolic risk factors.

While these medications are highly effective, they present barriers, particularly the need for sustained use to maintain benefits because discontinuation frequently results in weight regain and reversal of cardiometabolic improvements [10–13]. However, long-term use is often limited by factors including medication cost, inconsistent insurance coverage, adverse effects, or patient preference, leading to high discontinuation rates in real-world practice [14–16]. As use of these medications continues to expand, clinicians may increasingly face patients for whom long-term therapy is not feasible or desirable. Yet evidence-based guidance for dose reduction or discontinuation to preserve long-term weight-loss remains limited.

This review examines barriers to long-term GLP-1RA therapy and summarizes current evidence for strategies to support weight-loss maintenance following treatment reduction or discontinuation. Specifically, we discuss the rationale for dose reduction and personalized dosing approaches, the potential role of oral GLP-1RAs and alternative anti-obesity medications, patient selection considerations, and behavioral interventions to support durable treatment outcomes following successful GLP-1RA therapy. Although liraglutide was the first GLP-1RA approved for chronic weight management, semaglutide and tirzepatide have become the most widely used agents due to their greater efficacy and convenience of use (e.g., weekly vs daily injection) [17,18]. Therefore, the discussion throughout this review focuses primarily on semaglutide and tirzepatide to provide the most actionable and clinically relevant insights.

2. Barriers to Lifelong GLP-1RA Therapy

2.1. Cost and Access

A primary barrier to GLP-1RA use is their high cost due to a lack of insurance coverage and previously, supply shortages. Many insurance plans may place additional requirements for coverage (e.g., body mass index [BMI] > 35) or failure on a cheaper medication (e.g., phentermine-topiramate) [19,20]. Without insurance, self-pay costs for semaglutide and tirzepatide can range from \$299 to \$449 per month when purchased from direct-to-consumer platforms such as LillyDirect and NovoCare Pharmacy [21,22]. In response to their rapid rise in use, the FDA placed these drugs on the shortages list in 2022, permitting the use of compounded formulations [23]. Subsequently, many individuals turned to compounded versions for their lower price and greater availability. However, compounded formulations are not FDA-approved and therefore are not subject to the FDA's review for safety, efficacy, and quality [24]. Additionally, variability in compounding practices and limited clinician oversight raises concerns regarding accuracy, product quality, and risk of counterfeit products [23]. Further, following the resolution of the FDA-declared shortages, the agency clarified that compounded semaglutide and tirzepatide products that are essentially copies of commercially available FDA-approved products may violate sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, including some formulations containing additives such as vitamin B12. Considering these risks, the American Diabetes Association and Obesity Medicine Association advise against the use of compounded GLP-1RAs [25,26]. Because compounded GLP-1RA products are dispensed through multiple pharmacy pathways and are not systematically tracked, the prevalence of compounded GLP-1RA use remains difficult to quantify.

2.2. Heterogeneity of Response

Variability in weight loss response to GLP-1RA medications remains a significant and poorly understood challenge. Some individuals experience substantial weight reductions, while others demonstrate minimal response [27]. In the STEP-1 trial, 13.6% of participants receiving semaglutide failed to achieve at least 5% body weight loss after 68 weeks of treatment [8]. Similarly, in the SURMOUNT-1 trial, 15%, 11%, and 9% of participants receiving tirzepatide 5 mg, 10 mg, and 15 mg, respectively, did not achieve at least 5% weight loss after 72 weeks of treatment.⁹ This represents a presence of treatment under responders, while conversely, some individuals exhibit marked weight reductions and may be considered over responders [28]. Demographic and clinical characteristics

associated with greater weight loss include female sex, younger age, higher baseline body weight and waist circumference, lower baseline glycated hemoglobin (HbA1c) levels, and White or European ancestry [27–32]. Among postmenopausal women, use of hormone replacement therapy (HRT) has also been associated with greater weight loss in response to GLP-1RA therapy [33,34]. While these associations exist, the determinants of over- and under-response remain insufficiently defined, emphasizing the need for further investigation to better predict treatment efficacy.

2.2.1. Gastrointestinal Side Effects

Gastrointestinal adverse effects are among the most common side effects affecting long-term GLP-1RA adherence, with up to 25-40% of users experiencing nausea and 10-20% reporting vomiting, diarrhea, or constipation [8,9,35]. These symptoms are typically worst during treatment initiation and dose escalation [36] and have been reported as less severe for tirzepatide [37]. While not fully understood, these effects may be a result of delayed gastric emptying and changes to intestinal motility and transit time [38].

2.2.2. Nutritional Status

GLP-1RAs have been shown to reduce energy intake by 25-35% [39–41]; however, it remains unclear whether this reduction is accompanied by improvements in diet quality. Because obesity is associated with poor baseline diet quality [42], substantially lower energy intake without improved dietary quality may increase the risk of nutrient inadequacies. One cross-sectional study of dietary intake in GLP-1RA users reported inadequate intake of several essential nutrients and found that total Healthy Eating Index (HEI) scores fell significantly below the recommended targets, with no differences by duration of GLP-1RA use [43,44]. These findings suggest that poor diet quality may persist during GLP-1RA therapy and highlights the need for concurrent nutrition intervention to minimize nutrient inadequacies.

2.3. Real-World Persistence

Discontinuation rates of GLP-1RA medications are high, with real world estimates in the range of 50% to 75% within 12 months [15]. Many of the barriers discussed previously contribute to treatment discontinuation [14–16,45,46], which is problematic due to the rapid weight regain observed after stopping therapy. Those who discontinue GLP-1RA therapy regain 10-15% of body weight, representing nearly all weight lost during treatment^{10,11} and exhibit regression toward baseline levels of previously improved cardiometabolic markers [10–12].

Given these consequences, patients should be counseled before initiating GLP-1RA therapy that discontinuation frequently results in reversal of both weight loss and cardiometabolic improvements. Because gastrointestinal adverse events are a common reason for discontinuation, clinicians should also provide anticipatory guidance on symptom management. Current recommendations emphasize dietary and behavioral modifications, including smaller portion sizes, eating slowly, avoiding lying down after eating, and tailoring food composition to individual tolerance [47]. Monitoring specific foods and meal timings that exacerbate symptoms can also help improve tolerability and reduce discontinuation. Despite these measures, a substantial proportion of patients may ultimately discontinue treatment, highlighting the need for evidence-based strategies that support long-term weight loss maintenance.

3. Framework for Post GLP-1RA Weight-Loss Maintenance

Although current clinical guidelines recommend continued GLP-1RA therapy to maintain weight loss, they provide little guidance on how to manage patients who cannot or choose not to remain on treatment [13]. As a result, identifying strategies that preserve therapeutic benefits while reducing medication burden is an important priority. Rather than viewing discontinuation as the end of obesity treatment, clinicians should consider weight-loss maintenance as an active phase of clinical

management that requires individualized decision-making. As illustrated in Figure 1, multiple evidence-informed maintenance strategies may be considered based on treatment response, medication tolerability, body composition, cardiometabolic health, patient preferences, affordability, and long-term clinical goals. Potential approaches include personalized titration, reduced maintenance doses, intermittent dosing, or transition to alternative pharmacotherapies. Rather than abrupt cessation, these strategies aim to individualize treatment that balances efficacy, tolerability, cost, and long-term adherence and health maintenance, with the selection of a maintenance strategy guided by patient characteristics, treatment response, body composition, and clinical goals.

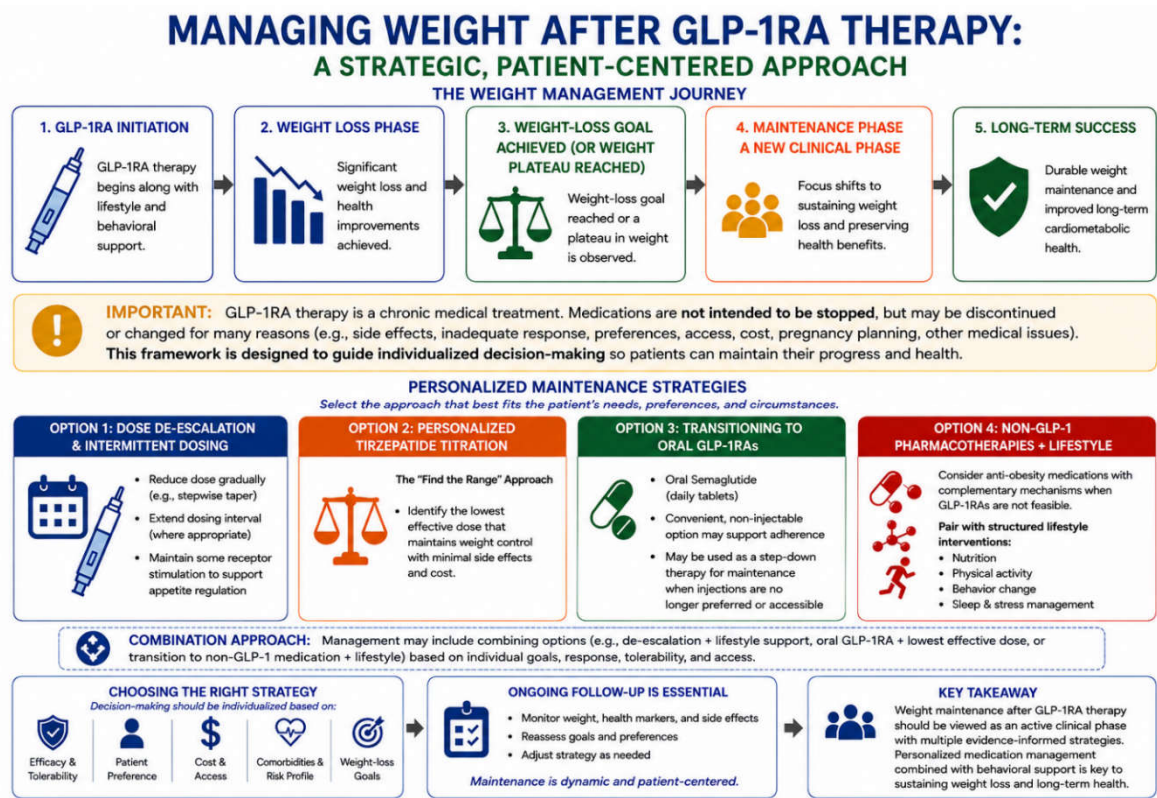


Figure 1. Managing Weight After GLP-1RA Therapy: A Strategic, Patient-Centered Approach. Following successful weight loss with glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy, weight-loss maintenance should be viewed as a distinct phase of obesity management requiring ongoing, individualized clinical decision-making. Although GLP-1RA therapy is intended as a chronic treatment, medication modification or discontinuation may occur because of treatment response, tolerability, patient preferences, access, cost, pregnancy planning, or other clinical considerations. After weight-loss goals are achieved (or a weight plateau is reached), clinical management should transition from an emphasis on weight reduction to individualized long-term weight-loss maintenance, with the goals of preserving weight loss, cardiometabolic health, and treatment adherence whenever appropriate. Potential maintenance strategies include dose de-escalation or intermittent dosing, personalized titration to the lowest effective dose, transition to oral GLP-1 receptor agonists, or transition to alternative anti-obesity pharmacotherapy combined with continued lifestyle and behavioral support. These approaches are not mutually exclusive, and long-term management may involve combining or sequentially implementing multiple strategies as patient needs, treatment response, and clinical circumstances evolve. Selection of an appropriate strategy should be individualized according to treatment response, medication tolerability, body composition, cardiometabolic health, patient preferences, affordability and access, and long-term clinical goals. Because maintenance needs may evolve over time, regular follow-up and reassessment are essential to optimize long-term outcomes and sustain the weight-loss and metabolic benefits achieved during GLP-1RA therapy.

4. Pharmacologic Maintenance Strategies

4.1. Personalized Dose Titration

Standard dosing protocols for GLP-1RAs involve gradual titration to the maximum dose. Semaglutide is initiated at 0.25 mg weekly for four weeks, followed by stepwise increases every four weeks (0.5, 1.0, 1.7, and 2.4 mg) to a recommended maintenance dose of 1.7 or 2.4 mg weekly [48]. Tirzepatide follows a similar structure, beginning at 2.5 mg weekly and increasing in 2.5-mg increments at four-week intervals to a maximum of 15 mg weekly [49]. Dose-response data from tirzepatide trials demonstrate weight loss of 12-15%, 18.7-19.5%, and 19.7-20.9% at 5-, 10-, and 15-mg doses, respectively [9,50]. Although comparable dose-response data for semaglutide is limited, tirzepatide findings suggest that lower doses may be sufficient for weight-loss maintenance in some individuals [9].

Emerging evidence also supports personalized dosing strategies that tailor treatment intensity to individual response rather than automatically escalating to the maximum dose. In a retrospective cohort study of participants enrolled in a digital weight loss program combining semaglutide and intensive behavioral therapy (IBT), dose escalation was generally deferred when participants maintained >0.5% weekly weight loss and reported adequate control of hunger and satiety [51]. Under this approach, the mean semaglutide dose was 1.08 mg/week with a mean body weight loss of 16.4% after 64 weeks of treatment. By comparison, the landmark trial of semaglutide efficacy, STEP-1, reported that 89.6% of participants received the full 2.4-mg maintenance dose to achieve a mean weight reduction of 14.9% over 68 weeks [8]. Together, these findings suggest that individualized titration based on treatment response and tolerability may achieve comparable weight-loss outcomes at a lower dose than those used in traditional escalation protocols. Therefore, clinicians should routinely assess both efficacy and tolerability when determining dose adjustments, as some individuals may achieve meaningful weight reduction at lower doses.

4.2. Reduced Maintenance Dose

Evidence from trials of maintenance dosing supports the feasibility of dose-reduction strategies. The SURMOUNT-MAINTAIN trial evaluated the effects of continuing tirzepatide at the maximum tolerated dose (MTD; 10 or 15 mg), reducing the dose to 5 mg, or discontinuing treatment following a 60-week weight-loss period, with participants subsequently followed during a 52-week maintenance phase.52 Participants who continued tirzepatide maintained greater weight reduction than those assigned to placebo, with mean percent weight changes in baseline body weight at week 112 of -21.9%, -16.6%, and -9.9% in the MTD, reduced dose, and placebo groups, respectively. Among participants who had achieved a weight loss plateau, those continuing tirzepatide at the MTD maintained 96.5% of weight loss achieved during the initial intervention period, whereas those transitioned to the reduced dose maintained 67.9% of prior weight loss, compared with 42.8% in the placebo group. Cardiometabolic biomarkers also improved in both tirzepatide groups relative to placebo. Although maintenance of weight reduction was greatest with continued MTD treatment, clinically meaningful weight-loss maintenance was still observed with the reduced-dose regimen. This is important, as lower doses are associated with fewer adverse effects and reduced cost, potentially addressing barriers to long-term treatment adherence, particularly for patients paying out-of-pocket.

4.3. Intermittent Dosing

Intermittent dosing represents another strategy to reduce reliance on continuous therapy. One retrospective case series evaluated reduced-frequency dosing for weight loss maintenance following a weight loss plateau. Frequency of dosing was guided by patient preference, with more than half of patients electing to administer treatment once every two weeks [53]. During the maintenance phase, patients experienced additional reductions in body weight beyond their initial plateau ($-2.3\% \pm 0.7\%$).

Improvements in metabolic syndrome-related parameters, including prediabetes, triglycerides, high-density lipoprotein (HDL) cholesterol, and blood pressure were also maintained with reduced frequency dosing. Additional support for this approach comes from a case report describing two individuals who maintained meaningful weight loss despite less frequent dosing [54]. One patient sustained weight reduction by self-administering 1.7-mg semaglutide every 10-14 days, while another maintained substantial weight loss despite frequent treatment interruptions caused by tirzepatide supply shortages. These cases suggest that intermittent dosing may preserve weight-loss in select patients. Further investigation is needed to determine the safety and efficacy of such approaches.

4.4. Oral GLP-1RAs

Aside from dose reduction strategies, patients discontinuing subcutaneous GLP-1RA therapy may benefit from transitioning to oral GLP-1RAs. Available options include oral semaglutide and orforglipron, which were FDA approved for weight management in 2025 and 2026, respectively. In a phase 3 randomized controlled trial of once-daily oral semaglutide, body weight reductions were 15.1% and 13.6% with the 50-mg and 25-mg doses, along with improvements in cardiometabolic risk factors [55,56]. Similarly, in a clinical trial of orforglipron, participants receiving the medication once daily for 72 weeks achieved mean weight reductions of 7.5%, 8.4% and 11.2% with the 6-, 12-, and 36-mg doses, respectively, while also demonstrating improvements in cardiometabolic risk factors [57]. Side effects of oral GLP-1RAs are predominantly gastrointestinal, including nausea, constipation, diarrhea, and vomiting [55,57]. Like subcutaneous therapies, these symptoms are usually worst during dose escalation.

For patients wishing to discontinue subcutaneous therapy while maintaining the benefits of GLP-1RA treatment, oral formulations may provide an attractive option. Additionally, for patients who have achieved the desired weight-loss goals, transitioning to a lower-dose oral GLP-1RA may represent a strategy for long-term weight loss maintenance while reducing the risk of excessive weight loss with highly effective subcutaneous therapies. One study evaluating maintenance therapy with orforglipron after reaching a weight loss plateau while using subcutaneous tirzepatide or semaglutide provides preliminary evidence for this approach [58]. Participants who transitioned to orforglipron maintained 74.7% of their initial weight loss following tirzepatide treatment compared with 49.2% in the placebo group (treatment difference, 25.5%). Among participants previously treated with semaglutide, those receiving orforglipron maintained 79.3% of their initial weight loss compared with 37.6% in the placebo group (treatment difference, 41.7%). Maintenance therapy with orforglipron also preserved the cardiometabolic improvements achieved during prior subcutaneous GLP-1RA treatment. Oral semaglutide may represent another potential maintenance option; however, to our knowledge, no studies have evaluated transitioning patients from subcutaneous GLP-1RA therapy to oral semaglutide. From a practical standpoint, orforglipron may offer greater convenience because it can be taken at any time of day without regard to meals [59], whereas oral semaglutide must be taken on an empty stomach with up to 4 oz of plain water, followed by at least a 30-minute interval before eating, drinking, or taking other oral medications [60].

4.5. Alternative Anti-Obesity Medications

Non-GLP-1 anti-obesity medications represent an additional maintenance option for patients seeking to discontinue GLP-1RA therapy and may offer advantages related to cost, accessibility, or tolerability. Available alternatives include phentermine-topiramate, naltrexone-bupropion, and orlistat. Among these, phentermine-topiramate is generally considered the preferred alternative. Phentermine, a sympathomimetic amine anorectic [61], and topiramate, an anticonvulsant with weak carbonic anhydrase-inhibiting and glutamate receptor-antagonist properties [62], act together to suppress appetite and enhance satiety. Clinical trials demonstrate mean weight loss of 8-10% of baseline body weight during the first year of treatment, compared with approximately 1.2% in placebo groups [63,64]. Weight-loss magnitude declines after one year; however, continued therapy

has been associated with long-term weight loss maintenance [65]. Additionally, phentermine-topiramate has been shown to reduce progression to T2DM in individuals with prediabetes or metabolic syndrome [66]. Common adverse effects include dry mouth, constipation, and paresthesia [63,64]. Despite these potential side effects, phentermine-topiramate remains a strong alternative for patients discontinuing GLP-1RA therapy because of its demonstrated efficacy in both weight loss and weight-loss maintenance.

Naltrexone-bupropion is considered a second-line pharmacotherapy for obesity, given its lower efficacy compared with GLP-1RAs and phentermine-topiramate, as well as its broader range of contraindications. Naltrexone, an opioid antagonist, is approved for treatment of alcoholism and opioid addiction [67,68], while bupropion is an antidepressant indicated for smoking cessation, depression, and seasonal affective disorder [69,70]. Their combined use is thought to promote weight loss through stimulation of hypothalamic pro-opiomelanocortin (POMC) neurons by bupropion and inhibition of opioid-mediated POMC autoinhibition by naltrexone [71]. Clinical trials demonstrate average weight loss of 4-5% compared with placebo [72-75]. The most common adverse effects include nausea, headaches, and constipation [72,73]. Although associated with broader contraindications, naltrexone-bupropion remains a viable option to support patients discontinuing GLP-1RA therapy.

Orlistat, another second-line pharmacotherapy for obesity, inhibits pancreatic lipase, reducing fat absorption and increasing fecal fat excretion [35]. Its use is limited by lower efficacy and high prevalence of gastrointestinal side effects. When combined with behavioral intervention, orlistat produces weight loss of 5-10 kg, compared to 3-6 kg achieved through behavioral intervention alone [76]. Common adverse effects include cramping, flatulence, fecal incontinence, oily spotting, and flatus with discharge, occurring in 15-30% of users [77,78]. While orlistat remains an available alternative to GLP-1RAs, its tolerability and lower efficacy make it less preferable than other pharmacologic options.

For patients seeking to discontinue subcutaneous GLP-1RA therapy and maintain weight-loss benefits, alternative pharmacotherapy may provide an effective strategy for maintaining weight-loss benefits. Oral GLP-1RAs may offer a means of preserving GLP-1 receptor agonism while improving convenience and accessibility, whereas phentermine-topiramate currently represents the most effective non-GLP-1 pharmacologic alternative. Medication selection should ultimately be individualized based on patient characteristics, contraindications, and treatment goals to ensure the most appropriate approach.

5. Patient Selection and Clinical Phenotyping

While evidence suggests that dose de-escalation and alternative maintenance strategies may preserve weight loss in some patients, these approaches may not be appropriate for everyone. Therefore, careful patient selection is critical, with maintenance strategies individualized according to treatment response, body composition, cardiometabolic health, treatment tolerability, affordability, and patient goals. Patients experiencing financial constraints, barriers to access, significant adverse effects, or excessive weight loss may be strong candidates for these strategies.

5.1. Cost, Access, and Treatment Tolerability

Medication cost remains a major barrier to sustained GLP-1RA use. Self-pay pricing for both subcutaneous and oral GLP-1RA therapies generally increase with dose, creating an opportunity for dose reduction to lower monthly treatment costs. For example, Lilly Direct prices tirzepatide from \$299/month for 2.5 mg to \$449/month for doses ≥ 7.5 mg, while Novo Nordisk prices semaglutide from \$199/month at lower doses to \$399/month at the highest available dose [21,79]. Similar dose-dependent pricing structures exist for oral GLP-1RA therapies, including oral semaglutide (\$149 for lower doses, \$299 for higher doses) and orforglipron (\$149-\$199 at lower doses, \$299 at higher doses) [79,80]. Alternative pharmacotherapies may also provide lower-cost treatment options, with approximate monthly self-pay costs of \$98 for phentermine-topiramate, \$99 for naltrexone

bupropion, and \$85 for orlistat [81–83]. In addition to cost savings, lower doses may improve treatment tolerability surrounding gastrointestinal side effects and reduce risk of abrupt discontinuation due to symptoms.

5.2. Assessing Achievement of Therapeutic Goals

Patients who have achieved targeted weight loss and/or cardiometabolic outcomes may also be candidates for dose reduction or transition to alternative pharmacotherapies. However, determining when weight loss is sufficient remains challenging. Although BMI is commonly used to classify weight status, it has well-recognized limitations because it does not directly measure adiposity and does not account for age, sex, or racial differences that influence body composition.⁸⁴ More recent clinical guidelines recommend confirming excess adiposity using additional anthropometric measures, such as waist circumference and waist-to-height ratio, alongside assessment of obesity-related complications and cardiometabolic risk factors [85,86]. Improvement in these measures may better identify patients who have achieved adequate therapeutic benefit and are appropriate candidates for weight-loss maintenance strategies, rather than relying on BMI alone. Additionally, assessing improvements in cardiometabolic labs and other risk factors (e.g., hypertension) provides a more comprehensive view of overall metabolic health. In tandem with these improvements, a patient should also demonstrate adequate physical activity and a healthy diet prior to dose reduction to improve likelihood of weight loss maintenance.

5.3. Identifying Excessive Weight Loss

Beyond achieving weight loss goals, consideration should also be given to excessive weight loss and its composition. Some individuals may be highly responsive to the medication and lose too much weight. Although defining excessive weight loss is challenging due to interindividual variability, assessment of BMI together with body composition may provide objective measures to inform individualized dose adjustments [87]. For example, patients who have reduced their BMI < 22 kg/m² or reduced body fat percentage to <10% in men or <15% in women may warrant consideration of dose reduction to prevent excessive weight loss [88].

5.4. Body Composition and Lean Mass Preservation

A physiologic consequence of weight loss is a reduction in lean mass. If excessive, this loss can impair muscle strength, physical function and metabolic rate, thereby increasing the risk of sarcopenia and weight regain [89,90]. Lean mass accounts for approximately 35.2% and 25.4% of total weight loss during semaglutide and tirzepatide treatment, respectively [91]. This proportion is comparable to that observed with other weight loss interventions, including bariatric surgery (20–30%) [92,93] and lifestyle intervention (26.2%) [91]. Although the relative proportion of lean mass loss appears similar across modalities, the greater total weight loss achieved with GLP-1RAs may result in larger absolute reductions in lean mass, particularly relative to lifestyle intervention alone. Preservation of lean mass is particularly important in populations at elevated risk for sarcopenia, including older adults, postmenopausal women, patients with chronic kidney disease, etc. [94]. For these populations, individualized approaches that prioritize not only the quantity, but also the quality of weight loss may be warranted. Potential strategies include slower rates of weight loss achieved through dose adjustment, progressive resistance training at least 2–3 times per week, adequate dietary protein intake (approximately 1.2–1.6 g/kg/day), and serial body composition assessment (e.g., dual-energy X-ray absorptiometry [DXA]) to monitor changes in fat and lean tissue over time [91].

5.5. Behavioral Strategies for Durable Weight-Loss Maintenance

Obesity is a chronic disease requiring individualized treatment strategies, and although pharmacologic approaches are effective, durable weight-loss maintenance will likely depend on

successful integration of medication management with behavioral intervention. Evidence from established weight loss interventions—including lifestyle modification and bariatric surgery—consistently identifies behavioral and psychological factors as the primary predictors of long-term weight loss maintenance. These include adherence to healthy dietary patterns, regular physical activity, and avoidance of maladaptive eating behaviors [95–97]. Although GLP-1RA therapy produces significant reductions in energy intake and body weight, it has not been shown to improve dietary quality or nutritional adequacy [43,44]. However, the changes in food related thoughts and behaviors during GLP-1RA therapy may offer a period where adoption of healthy behaviors may be more feasible.

Emerging evidence suggests that GLP-1RA therapy may create a behavioral window conducive to lasting habit formation, during which reduced hunger, food preoccupation, and maladaptive eating behaviors may increase receptivity to adopting sustainable dietary and lifestyle habits. Koide et al.⁹⁸ demonstrated that GLP-1RA treatment suppressed external eating—the tendency to eat in response to environmental cues rather than physiological hunger and satiety signals [99,100]—and reduced emotional eating scores during the first three months of therapy; however, emotional eating scores returned to baseline by 12 months. This transient attenuation of maladaptive eating behaviors may represent a period of heightened receptivity during which individuals more readily adopt healthy dietary habits. If these habits are established during a period of neuroplasticity, they may be more likely to persist after GLP-1RA discontinuation, potentially improving long-term weight loss maintenance. Integration of nutrition counseling from a nutrition professional during this behavioral window may help support patients in establishing personalized, sustainable dietary habits that persist independent of GLP-1RA therapy.

5.6. Future Directions

The chronicity of obesity means that some patients will be unable to discontinue GLP-1RA therapy while maintaining its benefits. However, the persistently high discontinuation rates highlight an urgent need to identify strategies that optimize patient outcomes when therapy is reduced or stopped. Because these medications are relatively new, research is still needed to characterize evolving prescribing and utilization patterns and to identify strategies that best support patients during and after treatment cessation.

First, the rapidly evolving landscape of GLP-1RA access warrants further investigation. Little is known about the proportion of patients obtaining these medications through compounding pharmacies or how this has changed over time. Quantifying the prevalence of compounded GLP-1RA use and identifying the populations most likely to rely on these products will improve understanding of real-world treatment patterns, medication access, and safety.

From a pharmacologic perspective, future studies should evaluate the efficacy of tapering approaches, including dose de-escalation and intermittent dosing, in reducing weight regain. Research is also needed to determine whether alternative anti-obesity medications can help preserve weight loss apart from GLP-1RA therapy. With the emergence of oral GLP-1RA formulations, research should examine the feasibility of transitioning from subcutaneous to oral therapy, including dose-conversion strategies and their effectiveness for long-term weight maintenance. Finally, the potential for personalized dosing strategies warrants further investigation. To do so, it is important to understand factors that distinguish over-responders from under-responders to enable more precise titrations and improve individual outcomes.

Lifestyle interventions represent another critical area for future research. Future studies should also determine when maintenance interventions should begin and how behavioral and pharmacologic strategies can be integrated to maximize long-term success. Studies should examine the implementation of behavioral, dietary, and physical activity intervention during active GLP-1RA therapy to determine whether early adoption enhances long-term maintenance after medication cessation. Leveraging the period of improved appetite regulation during pharmacological treatment

may enable the formation of sustainable habits that persist once therapy is withdrawn, improving long-term weight loss maintenance.

5.7. Conclusions

GLP-1RAs have transformed obesity treatment by producing clinically meaningful weight loss, however, long-term treatment is not feasible for all patients because of cost, access barriers, adverse effects, patient preference, etc. Discontinuation is associated with weight regain and loss of metabolic benefit, highlighting a critical need for evidence-based maintenance strategies. Ultimately, successful long-term obesity management will require individualized approaches that integrate pharmacologic and lifestyle interventions. Future prospective studies are needed to identify patients most likely to benefit from these strategies and to establish evidence-based guidelines that support durable weight-loss maintenance following GLP-1RA therapy. Advancing this evidence will support recognition of weight-loss maintenance as an active, individualized phase of obesity care, providing a more equitable, sustainable, and patient-centered framework for the use of GLP-1RA therapy in obesity care.

Funding: No funding was received for the preparation of this manuscript.

Acknowledgments: ChatGPT was used to assist with language development and figure creation. The authors take full responsibility for all content, interpretations, and accuracy.

Conflicts of Interest: The authors declare no conflicts of interest related to this work.

Abbreviations

GLP-1RA	Glucagon-like peptide-1 receptor agonist
GIP	Glucose-dependent insulintropic polypeptide
HbA1c	Hemoglobin A1c
HRT	Hormone replacement therapy
BMI	Body mass index
HEI	Healthy Eating Index
T2DM	Type 2 diabetes mellitus
MTD	Maximum tolerated dose
IBT	Intensive behavioral therapy
HDL	High-density lipoprotein
POMC	Pro-opiomelanocortin
DXA	Dual-energy X-ray absorptiometry

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